

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America  
NEWS 2 "Ask CAS" for self-help around the clock  
NEWS 3 DEC 05 CASREACT(R) - Over 10 million reactions available  
NEWS 4 DEC 14 2006 MeSH terms loaded in MEDLINE/LMEDLINE  
NEWS 5 DEC 14 2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER  
NEWS 6 DEC 14 CA/CAPLUS to be enhanced with updated IPC codes  
NEWS 7 DEC 21 IPC search and display fields enhanced in CA/CAPLUS with the  
IPC reform  
NEWS 8 DEC 23 New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/  
USPAT2  
NEWS 9 JAN 13 IPC 8 searching in IFIPAT, IFIUDb, and IFICDB  
NEWS 10 JAN 13 New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to  
INPADOC  
NEWS 11 JAN 17 Pre-1988 INPI data added to MARPAT  
NEWS 12 JAN 17 IPC 8 in the WPI family of databases including WPIFV  
  
NEWS EXPRESS JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,  
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.  
V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT  
<http://download.cas.org/express/v8.0-Discover/>  
  
NEWS HOURS STN Operating Hours Plus Help Desk Availability  
NEWS INTER General Internet Information  
NEWS LOGIN Welcome Banner and News Items  
NEWS PHONE Direct Dial and Telecommunication Network Access to STN  
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that  
specific topic.

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research. Use for software development or design or implementation  
of commercial gateways or other similar uses is prohibited and may  
result in loss of user privileges and other penalties.

\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 10:38:24 ON 23 JAN 2006

=> file dissab

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'DISSABS' ENTERED AT 10:38:39 ON 23 JAN 2006

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FILE COVERS 1861 TO 20 DEC 2005 (20051220/ED)

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```
=> s melanin
      261 MELANIN
      20 MELANINS
L1      267 MELANIN
      (MELANIN OR MELANINS)
```

```
=> s 6D2
L2      1 6D2
```

```
=> s l2 and l1
L3      1 L2 AND L1
```

```
=> d ibib 1
```

```
L3  ANSWER 1 OF 1  DISSABS COPYRIGHT (C) 2006 ProQuest Information and
      Learning Company; All Rights Reserved on STN
ACCESSION NUMBER:  2005:39050, DISSABS  Order Number: AAI3155910
TITLE:            Function and secretion of Cryptococcus neoformans virulence
                  factors glucuronoxylomannan and laccase
AUTHOR:           Garcia Rivera, Javier [Ph.D.]; Casadevall, Arturo [advisor]
CORPORATE SOURCE: Yeshiva University (0266)
SOURCE:           Dissertation Abstracts International, (2005) Vol. 65, No.
                  12B, p. 6175. Order No.: AAI3155910. 162 pages.
                  ISBN: 0-496-16470-8.
DOCUMENT TYPE:    Dissertation
FILE SEGMENT:     DAI
LANGUAGE:         English
ENTRY DATE:       Entered STN: 20050826
                  Last Updated on STN: 20050826
```

```
=>
```

```
---Logging off of STN---
```

```
=>
Executing the logoff script...
```

```
=> LOG Y
```

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.66	1.87

STN INTERNATIONAL LOGOFF AT 10:39:24 ON 23 JAN 2006

Connection closed by remote host

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

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NEWS 6 DEC 14 CA/CAPLUS to be enhanced with updated IPC codes  
NEWS 7 DEC 21 IPC search and display fields enhanced in CA/CAPLUS with the  
IPC reform  
NEWS 8 DEC 23 New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/  
USPAT2  
NEWS 9 JAN 13 IPC 8 searching in IFIPAT, IFIUDB, and IFICDB  
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INPADOC  
NEWS 11 JAN 17 Pre-1988 INPI data added to MARPAT  
NEWS 12 JAN 17 IPC 8 in the WPI family of databases including WPIFV  
  
NEWS EXPRESS JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,  
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.  
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NEWS INTER General Internet Information  
NEWS LOGIN Welcome Banner and News Items  
NEWS PHONE Direct Dial and Telecommunication Network Access to STN  
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006

=> file medline

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006

FILE LAST UPDATED: 21 JAN 2006 (20060121/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 will soon be available. For details on the 2005 reload, enter HELP RLOAD at an arrow prompt (=>).  
See also:

<http://www.nlm.nih.gov/mesh/>  
[http://www.nlm.nih.gov/pubs/techbull/nd04/nd04\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html)  
[http://www.nlm.nih.gov/pubs/techbull/nd05/nd05\\_med\\_data\\_changes.html](http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html)  
[http://www.nlm.nih.gov/pubs/techbull/nd05/nd05\\_2006\\_MeSH.html](http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html)

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate

=> s melanin

```
      7148 MELANIN
      6333 MELANINS
L1      9970 MELANIN
      (MELANIN OR MELANINS)
```

=> s melanoma

```
      60502 MELANOMA
      9282 MELANOMAS
      80 MELANOMATA
      1 MELANOMATAS
L2      61483 MELANOMA
      (MELANOMA OR MELANOMAS OR MELANOMATA OR MELANOMATAS)
```

=> s l2 and l1

```
L3      2328 L2 AND L1
```

=> s antibod?

```
L4      705098 ANTIBOD?
```

=> s l3 and l4

```
L5      198 L3 AND L4
```

=> s anti (W2) melanin

MISSING OPERATOR 'ANTI (W2'

The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

=> s anti (N2) melanin

MISSING OPERATOR 'ANTI (N2'

The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

=> s anti (2w) melanin

```
      589948 ANTI
      6 ANTIS
      589952 ANTI
      (ANTI OR ANTIS)
      7148 MELANIN
      6333 MELANINS
      9970 MELANIN
      (MELANIN OR MELANINS)
L6      7 ANTI (2W) MELANIN
```

=> s 16 and 12  
L7 2 L6 AND L2

=> d ibib 1-2

L7 ANSWER 1 OF 2 MEDLINE on STN  
ACCESSION NUMBER: 92335128 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 1631018  
TITLE: Response of transformed and normal mouse cell lines to  
anti-melanin compounds, hyperthermia, and  
radiation.  
AUTHOR: Raaphorst G P; Azzam E I  
CORPORATE SOURCE: Ottawa Regional Cancer Centre, Ontario, Canada.  
SOURCE: Pigment cell research / sponsored by the European Society  
for Pigment Cell Research and the International Pigment  
Cell Society, (1992 Feb) 5 (1) 25-9.  
Journal code: 8800247. ISSN: 0893-5785.  
PUB. COUNTRY: Denmark  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199208  
ENTRY DATE: Entered STN: 19920904  
Last Updated on STN: 19970203  
Entered Medline: 19920820

L7 ANSWER 2 OF 2 MEDLINE on STN  
ACCESSION NUMBER: 88107389 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 3426925  
TITLE: Radiation, heat and anti-melanin drug  
response of a transformed mouse embryo cell line with  
varying melanin content.  
AUTHOR: Raaphorst G P; Azzam E I  
CORPORATE SOURCE: Ottawa Regional Cancer Center, Ontario, Canada.  
SOURCE: British journal of cancer, (1987 Nov) 56 (5) 622-4.  
Journal code: 0370635. ISSN: 0007-0920.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198803  
ENTRY DATE: Entered STN: 19900305  
Last Updated on STN: 19900305  
Entered Medline: 19880309

=> s 17 and 14  
L8 0 L7 AND L4

=> file caplus  
COST IN U.S. DOLLARS  
FULL ESTIMATED COST

	SINCE FILE ENTRY	TOTAL SESSION
	1.90	2.11

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
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FILE COVERS 1907 - 23 Jan 2006 VOL 144 ISS 5  
FILE LAST UPDATED: 22 Jan 2006 (20060122/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

<http://www.cas.org/infopolicy.html>

=> s melanin

9775 MELANIN

7167 MELANINS

L9 11188 MELANIN

(MELANIN OR MELANINS)

=> s cancer or tumor or neoplas? or melanoma?

267591 CANCER

38666 CANCERS

277754 CANCER

(CANCER OR CANCERS)

359426 TUMOR

142769 TUMORS

405092 TUMOR

(TUMOR OR TUMORS)

435881 NEOPLAS?

30616 MELANOMA?

L10 690010 CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?

=> s 19 (1) l10

L11 1762 L9 (L) L10

=> s antibod?

L12 451938 ANTIBOD?

=> s l11 and l12

L13 60 L11 AND L12

=> s 13 (1) 19

PROXIMITY OPERATION NOT ALLOWED

Certain operators may not be nested in combination with other operators. A nested operator is valid only when it occurs at the same level or above the operator outside the nested phrase as determined by the following precedence list:

1. Numeric
2. (W), (NOTW), (A), (NOTA)
3. (S), (NOTS)
4. (P), (NOTP)
5. (L), (NOTL)
6. AND, NOT
7. OR

For example, '(MONOCLONAL(W)ANTIBOD?)(L)ANTIGEN?' is valid since (W) is above (L) on the precedence list. However, '((THIN(W)LAYER)(L)PHOSPHOLIPID#)(A)LACTONE#' is not valid since (L) is below (A) on the precedence list. The only exception is the 'OR' operator. This operator may be used in combination with any other operator. For example, '(ATOMIC OR NUCLEAR)(W)REACTOR' is valid.

```
=> s 19 (1) 112
L14      190 L9 (L) L12

=> s 114 and 110
L15      59 L14 AND L10

=> s 114 and 113
L16      53 L14 AND L13

=> s 116 not py>2002
      3463589 PY>2002
L17      45 L16 NOT PY>2002

=> d ibib 1-3
```

```
L17 ANSWER 1 OF 45 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:      2001:711229 CAPLUS
DOCUMENT NUMBER:      136:4079
TITLE:      Abnormal translocation of tyrosinase and
      tyrosinase-related protein 1 in cutaneous melanocytes
      of Hermansky-Pudlak syndrome and in melanoma cells
      transfected with anti-sense HPS1 cDNA
AUTHOR(S):      Sarangarajan, Rangaprasad; Budev, Ashish; Zhao, Yang;
      Gahl, William A.; Boissy, Raymond E.
CORPORATE SOURCE:      Department of Dermatology, University of Cincinnati,
      Cincinnati, OH, USA
SOURCE:      Journal of Investigative Dermatology (2001), 117(3),
      641-646
      CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER:      Blackwell Science, Inc.
DOCUMENT TYPE:      Journal
LANGUAGE:      English
REFERENCE COUNT:      12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
      RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
```

```
L17 ANSWER 2 OF 45 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:      2000:597655 CAPLUS
DOCUMENT NUMBER:      133:249026
TITLE:      Studies on epidermis reconstructed with and without
      melanocytes: melanocytes prevent sunburn cell
      formation but not appearance of DNA damaged cells in
      fair-skinned caucasians
AUTHOR(S):      Cario-Andre, Muriel; Pain, Catherine; Gall, Yvon;
      Ginestar, Jose; Nikaido, Osamu; Taieb, Alain
CORPORATE SOURCE:      Unite de Dermatologie, Universite Victor Segalen
      Bordeaux II, Bordeaux, 33076, Fr.
SOURCE:      Journal of Investigative Dermatology (2000), 115(2),
      193-199
      CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER:      Blackwell Science, Inc.
DOCUMENT TYPE:      Journal
LANGUAGE:      English
REFERENCE COUNT:      45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
      RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
```

```
L17 ANSWER 3 OF 45 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:      2000:380955 CAPLUS
DOCUMENT NUMBER:      134:39063
TITLE:      T311 - an anti-tyrosinase monoclonal antibody
      for the detection of melanocytic lesions in paraffin
      embedded tissues
AUTHOR(S):      Jungbluth, Achim A.; Iversen, Kristin; Coplan, Keren;
      Kolb, Denise; Stockert, Elisabeth; Chen, Yao-Tseng;
      Old, Lloyd J.; Busam, Klaus
```

CORPORATE SOURCE: Ludwig Institute for Cancer Research at Memorial  
Sloan-Kettering Cancer, New York, NY, 10021, USA  
SOURCE: Pathology, Research and Practice (2000), 196(4),  
235-242  
CODEN: PARPDS; ISSN: 0344-0338  
PUBLISHER: Urban & Fischer Verlag  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006

L1 9970 S MELANIN  
L2 61483 S MELANOMA  
L3 2328 S L2 AND L1  
L4 705098 S ANTIBOD?  
L5 198 S L3 AND L4  
L6 7 S ANTI (2W) MELANIN  
L7 2 S L6 AND L2  
L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006

L9 11188 S MELANIN  
L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?  
L11 1762 S L9 (L) L10  
L12 451938 S ANTIBOD?  
L13 60 S L11 AND L12  
L14 190 S L9 (L) L12  
L15 59 S L14 AND L10  
L16 53 S L14 AND L13  
L17 45 S L16 NOT PY>2002

=> s in vivo

413660 VIVO  
2 VIVOS  
L18 413661 IN VIVO  
(VIVO OR VIVOS)

=> s l18 and l17

L19 3 L18 AND L17

=> d ibib 1-3

L19 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:597655 CAPLUS

DOCUMENT NUMBER: 133:249026

TITLE: Studies on epidermis reconstructed with and without  
melanocytes: melanocytes prevent sunburn cell  
formation but not appearance of DNA damaged cells in  
fair-skinned caucasians

AUTHOR(S): Cario-Andre, Muriel; Pain, Catherine; Gall, Yvon;  
Ginestar, Jose; Nikaido, Osamu; Taieb, Alain

CORPORATE SOURCE: Unite de Dermatologie, Universite Victor Segalen  
Bordeaux II, Bordeaux, 33076, Fr.

SOURCE: Journal of Investigative Dermatology (2000), 115(2),  
193-199

CODEN: JIDEAE; ISSN: 0022-202X

PUBLISHER: Blackwell Science, Inc.

DOCUMENT TYPE: Journal



LANGUAGE: English  
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2000:304007 CAPLUS  
DOCUMENT NUMBER: 134:191455  
TITLE: gp100 mRNA is more sensitive than tyrosinase mRNA for  
RT-PCR amplification to detect circulating melanoma  
cells in peripheral blood of melanoma patients  
AUTHOR(S): Tsukamoto, K.; Ueda, M.; Hirata, S.; Osada, A.;  
Kitamura, R.; Takahashi, T.; Ichihashi, M.; Shimada,  
S.  
CORPORATE SOURCE: Nakakoma, Tamaho, 1110 Shimokato, Department of  
Dermatology, Yamanashi Medical University, Yamanashi,  
Japan  
SOURCE: Journal of Dermatological Science (2000), 23(2),  
126-131  
CODEN: JDSCEI; ISSN: 0923-1811  
PUBLISHER: Elsevier Science Ireland Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 1988:143024 CAPLUS  
DOCUMENT NUMBER: 108:143024  
TITLE: Cyclic AMP induces differentiation in vitro of human  
melanoma cells  
AUTHOR(S): Giuffre, Laura; Schreyer, Magali; Mach, Jean Pierre;  
Carrel, Stefan  
CORPORATE SOURCE: Ludwig Inst. Cancer Res., Epalinges, CH-1066, Switz.  
SOURCE: Cancer (New York, NY, United States) (1988), 61(6),  
1132-41  
CODEN: CANCAR; ISSN: 0008-543X  
DOCUMENT TYPE: Journal  
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006

L1 9970 S MELANIN  
L2 61483 S MELANOMA  
L3 2328 S L2 AND L1  
L4 705098 S ANTIBOD?  
L5 198 S L3 AND L4  
L6 7 S ANTI (2W) MELANIN  
L7 2 S L6 AND L2  
L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006

L9 11188 S MELANIN  
L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?  
L11 1762 S L9 (L) L10  
L12 451938 S ANTIBOD?  
L13 60 S L11 AND L12  
L14 190 S L9 (L) L12  
L15 59 S L14 AND L10  
L16 53 S L14 AND L13  
L17 45 S L16 NOT PY>2002

L18 413661 S IN VIVO  
L19 3 S L18 AND L17

=> s l17 and label?  
426929 LABEL?  
L20 4 L17 AND LABEL?

=> d ibib 1-4

L20 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 1998:426503 CAPLUS  
DOCUMENT NUMBER: 129:201389  
TITLE: Comparative immunohistochemical estrogen receptor  
analysis in primary and metastatic uveal melanoma  
AUTHOR(S): Makitie, Teemu; Tarkkanen, Ahti; Kivela, Tero  
CORPORATE SOURCE: Ophthalmic Pathology Laboratory, Department of  
Ophthalmology, Helsinki University Central Hospital,  
Hyks, FIN-00029, Finland  
SOURCE: Graefe's Archive for Clinical and Experimental  
Ophthalmology (1998), 236(6), 415-419  
CODEN: GACODL; ISSN: 0721-832X  
PUBLISHER: Springer-Verlag  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 1994:188128 CAPLUS  
DOCUMENT NUMBER: 120:188128  
TITLE: The mouse brown (b) locus protein has dopachrome  
tautomerase activity and is located in lysosomes in  
transfected fibroblasts  
AUTHOR(S): Winder, Alison J.; Wittbjør, Anna; Rosengren, Evald;  
Rorsman, Hans  
CORPORATE SOURCE: Sir William Dunn Sch. Pathol., Univ. Oxford Rd,  
Oxford, OX1 3RE, UK  
SOURCE: Journal of Cell Science (1993), 106(1), 153-66  
CODEN: JNCSAI; ISSN: 0021-9533  
DOCUMENT TYPE: Journal  
LANGUAGE: English

L20 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 1992:4874 CAPLUS  
DOCUMENT NUMBER: 116:4874  
TITLE: Monoclonal antibody against a melanosomal  
protein in melanotic and amelanotic human melanoma  
cells  
AUTHOR(S): McEwan, Max; Parsons, Peter G.; Moss, Denis J.;  
Burrows, Scott; Stenzel, Debbie; Bishop, Chris J.;  
Strutton, Geoffrey M.  
CORPORATE SOURCE: Queensland Inst. Medical Res., Herston, 4006,  
Australia  
SOURCE: Pigment Cell Research (1989), 2(1), 1-7  
CODEN: PCREEA; ISSN: 0893-5785  
DOCUMENT TYPE: Journal  
LANGUAGE: English

L20 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 1979:609110 CAPLUS  
DOCUMENT NUMBER: 91:209110  
TITLE: Demonstration and isolation of murine  
melanoma-associated antigenic surface proteins  
AUTHOR(S): Gersten, Douglas M.; Marchalonis, John J.

CORPORATE SOURCE: Frederick Cancer Res. Cent., Natl. Cancer Inst.,  
Frederick, MD, 21701, USA  
SOURCE: Biochemical and Biophysical Research Communications  
(1979), 90(3), 1015-24  
CODEN: BBRCA9; ISSN: 0006-291X  
DOCUMENT TYPE: Journal  
LANGUAGE: English

=> d abs 3

L20 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
AB BALB/c mice were immunized with tyrosinase, partially purified in 2 stages from a human melanoma cell line. A hybridoma was obtained which produced monoclonal antibody (MoAb 1C11) reactive with 8/10 melanoma cell lines and 10/10 primary cultures of human melanocytes, neval cells, and melanomas. Immunoreactivity correlated to a certain extent with tyrosinase activity but not with melanin content. No crossreactivity was obtained with neuroblastoma, medulloblastoma, fibroblasts, keratinocytes, lymphoid cells, or murine melanomas. Purification of the antigen directly from cell lysates with a MoAb 1C11 CNBr-Sepharose affinity column gave a green-brown protein of 56 kDa with no detectable tyrosinase activity. This protein was therefore different from 60 kDa active tyrosinase, identified by enzyme activity and Western blotting with a MoAb derived previously (MoAb 5C12). Unlike 5C12, 1C11 reactivity was not destroyed by pretreatment of the antigen with periodate. Immunogold labeling showed that the 1C11-reactive antigen was associated with melanosomes, and there was close correlation between 5C12 and 1C11 reactivity in resistance to trypsin and in staining various melanocytic cell populations. MoAb 1C11 may therefore recognize a polypeptide epitope in a mol. closely linked to melanin biosynthesis.

=> 6D2

6D2 IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system.  
For a list of commands available to you in the current file, enter  
"HELP COMMANDS" at an arrow prompt (=>).

=> s 6D2

L21 46 6D2

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006

L1 9970 S MELANIN  
L2 61483 S MELANOMA  
L3 2328 S L2 AND L1  
L4 705098 S ANTIBOD?  
L5 198 S L3 AND L4  
L6 7 S ANTI (2W) MELANIN  
L7 2 S L6 AND L2  
L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006

L9 11188 S MELANIN  
L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?  
L11 1762 S L9 (L) L10  
L12 451938 S ANTIBOD?  
L13 60 S L11 AND L12  
L14 190 S L9 (L) L12

L15 59 S L14 AND L10  
L16 53 S L14 AND L13  
L17 45 S L16 NOT PY>2002  
L18 413661 S IN VIVO  
L19 3 S L18 AND L17  
L20 4 S L17 AND LABEL?  
L21 46 S 6D2

=> s l21 and l10

L22 2 L21 AND L10

=> d ibib 1-2

L22 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:888105 CAPLUS

DOCUMENT NUMBER: 142:2821

TITLE: Dead cells in melanoma tumors  
provide abundant antigen for targeted delivery of  
ionizing radiation by a mAb to melanin

AUTHOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li;  
Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk,  
Jerome S.; Casadevall, Arturo

CORPORATE SOURCE: Department of Nuclear Medicine, Albert Einstein  
College of Medicine, Bronx, NY, 10461, USA

SOURCE: Proceedings of the National Academy of Sciences of the  
United States of America (2004), 101(41), 14865-14870  
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:577867 CAPLUS

DOCUMENT NUMBER: 119:177867

TITLE: A heparan sulfate proteoglycan in developing avian  
axonal tracts

AUTHOR(S): Halfter, Willi

CORPORATE SOURCE: Dep. Neurobiol., Univ. Pittsburgh, Pittsburgh, PA,  
15261, USA

SOURCE: Journal of Neuroscience (1993), 13(7), 2863-73

CODEN: JNRSDS; ISSN: 0270-6474

DOCUMENT TYPE: Journal

LANGUAGE: English

=> d kwic 2

L22 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

AB . . . immunized with embryonic chick retina basal lamina (clones 3A 12,  
3A3, and 9E 10) and embryonic chick optic tract (clone 6D2).

Cross-reactivity of all 4 antibodies were directed to the same antigen.

Antibodies to heparan sulfate proteoglycan from embryonic chick muscle or  
EHS mouse tumor (perlecan) did not cross-react with the neuronal  
heparan sulfate proteoglycan, suggesting that the 2 proteoglycans are not  
related. In Western. . .

=> s anti (2W) melanin

393809 ANTI

9 ANTIS

393816 ANTI

(ANTI OR ANTIS)

9775 MELANIN  
7167 MELANINS  
11188 MELANIN  
(MELANIN OR MELANINS)

L23 14 ANTI (2W) MELANIN

=> s l23 and antibod?  
451938 ANTIBOD?

L24 7 L23 AND ANTIBOD?

=> d ibib 1-7

L24 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:888105 CAPLUS

DOCUMENT NUMBER: 142:2821

TITLE: Dead cells in melanoma tumors provide abundant antigen for targeted delivery of ionizing radiation by a mAb to melanin

AUTHOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li; Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk, Jerome S.; Casadevall, Arturo

CORPORATE SOURCE: Department of Nuclear Medicine, Albert Einstein College of Medicine, Bronx, NY, 10461, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2004), 101(41), 14865-14870  
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:654728 CAPLUS

DOCUMENT NUMBER: 141:186978

TITLE: Radiolabeled antibodies for treatment of tumors

INVENTOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Casadevall, Arturo

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 23 pp.  
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004156780	A1	20040812	US 2004-775869	20040210
PRIORITY APPLN. INFO.:			US 2003-446684P	P 20030211

L24 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:339308 CAPLUS

DOCUMENT NUMBER: 141:136788

TITLE: Production of melanin by Aspergillus fumigatus

AUTHOR(S): Youngchim, Sirida; Morris-Jones, Rachael; Hay, Roderick J.; Hamilton, Andrew J.

CORPORATE SOURCE: Dermatology Department, St Johns Institute of Dermatology, Guy's Hospital, Kings and St Thomas' Medical Schools, London, UK

SOURCE: Journal of Medical Microbiology (2004), 53(3), 175-181  
CODEN: JMMIAV; ISSN: 0022-2615

PUBLISHER: Society for General Microbiology

DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 2002:639215 CAPLUS  
 DOCUMENT NUMBER: 137:307123  
 TITLE: Histoplasma capsulatum synthesizes melanin-like pigments in vitro and during mammalian infection  
 AUTHOR(S): Nosanchuk, Joshua D.; Gomez, Beatriz L.; Youngchim, Sirida; Diez, Soraya; Aisen, Philip; Zancope-Oliveira, Rosely M.; Restrepo, Angela; Casadevall, Arturo; Hamilton, Andrew J.  
 CORPORATE SOURCE: Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, 10461, USA  
 SOURCE: Infection and Immunity (2002), 70(9), 5124-5131  
 CODEN: INFIBR; ISSN: 0019-9567  
 PUBLISHER: American Society for Microbiology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 2000:457194 CAPLUS  
 DOCUMENT NUMBER: 133:85156  
 TITLE: Human melanin concentrating hormone receptor MCH1 and cDNA and diagnostic and therapeutic uses thereof  
 INVENTOR(S): Salon, John A.; Laz, Thomas M.; Nagorny, Raisa; Wilson, Amy E.  
 PATENT ASSIGNEE(S): Synaptic Pharmaceutical Corporation, USA  
 SOURCE: PCT Int. Appl., 173 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 4  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039279	A2	20000706	WO 1999-US31169	19991230
WO 2000039279	A3	20001102		
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 6221613	B1	20010424	US 1998-224426	19981231
CA 2358687	AA	20000706	CA 1999-2358687	19991230
AU 2000033430	A5	20000731	AU 2000-33430	19991230
AU 774398	B2	20040624		
EP 1141020	A2	20011010	EP 1999-969993	19991230
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2002533116	T2	20021008	JP 2000-591172	19991230
US 6221616	B1	20010424	US 2000-478601	20000106
US 6291195	B1	20010918	US 2000-478602	20000106
US 2002111306	A1	20020815	US 2001-885478	20010620
US 6723552	B2	20040420		

US 2003082623	A1	20030501	US 2001-899732	20010705
US 2003077701	A1	20030424	US 2001-29314	20011220
US 2004038855	A1	20040226	US 2003-341751	20030114
US 2004248173	A1	20041209	US 2004-825581	20040415
PRIORITY APPLN. INFO.:			US 1998-224426	A2 19981231
			WO 1999-US31169	W 19991230
			US 2000-610635	A2 20000705
			US 2001-885478	A1 20010620
			US 2001-899732	A1 20010705

L24 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:408610 CAPLUS  
DOCUMENT NUMBER: 131:180636  
TITLE: Structure and function of human prepro-orexin gene  
AUTHOR(S): Sakurai, Takeshi; Moriguchi, Takashi; Furuya, Keiko;  
Kajiwara, Noriko; Nakamura, Toshiaki; Yanagisawa,  
Masashi; Goto, Katsutoshi  
CORPORATE SOURCE: Institute of Basic Medical Sciences, University of  
Tsukuba, Tsukuba, 305-8575, Japan  
SOURCE: Journal of Biological Chemistry (1999), 274(25),  
17771-17776  
CODEN: JBCHA3; ISSN: 0021-9258  
PUBLISHER: American Society for Biochemistry and Molecular  
Biology  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:465553 CAPLUS  
DOCUMENT NUMBER: 115:65553  
TITLE: Mammalian melanin-concentrating hormones (MCHs) and  
methods of treatment using same  
INVENTOR(S): Vaughan, Joan; Fischer, Wolfgang Hermann; Rivier, Jean  
Edouard; Nahon, Jean Louis Marie; Presse, Francoise  
Genevieve; Vale, Wylie Walker, Jr.  
PATENT ASSIGNEE(S): Salk Institute for Biological Studies, USA  
SOURCE: PCT Int. Appl., 47 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 9011295	A1	19901004	WO 1990-US1492	19900320
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
US 5049655	A	19910917	US 1989-326984	19890322
CA 2046900	AA	19900923	CA 1990-2046900	19900320
CA 2046900	C	20000822		
EP 464105	A1	19920108	EP 1990-905279	19900320
EP 464105	B1	19960814		
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
JP 04503812	T2	19920709	JP 1990-505271	19900320
JP 2944202	B2	19990830		
AT 141288	E	19960815	AT 1990-905279	19900320
US 5449766	A	19950912	US 1994-208531	19940309
US 5530095	A	19960625	US 1995-447613	19950523
PRIORITY APPLN. INFO.:			US 1989-326984	A 19890322
			WO 1990-US1492	W 19900320
			US 1991-733660	B3 19910722

OTHER SOURCE(S):

MARPAT 115:65553

US 1994-208531

A3 19940309

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006

L1 9970 S MELANIN  
L2 61483 S MELANOMA  
L3 2328 S L2 AND L1  
L4 705098 S ANTIBOD?  
L5 198 S L3 AND L4  
L6 7 S ANTI (2W) MELANIN  
L7 2 S L6 AND L2  
L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006

L9 11188 S MELANIN  
L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?  
L11 1762 S L9 (L) L10  
L12 451938 S ANTIBOD?  
L13 60 S L11 AND L12  
L14 190 S L9 (L) L12  
L15 59 S L14 AND L10  
L16 53 S L14 AND L13  
L17 45 S L16 NOT PY>2002  
L18 413661 S IN VIVO  
L19 3 S L18 AND L17  
L20 4 S L17 AND LABEL?  
L21 46 S 6D2  
L22 2 S L21 AND L10  
L23 14 S ANTI (2W) MELANIN  
L24 7 S L23 AND ANTIBOD?

=> s l24 and l10

L25 3 L24 AND L10

=> de ibib 1-3

DE IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system.

For a list of commands available to you in the current file, enter

"HELP COMMANDS" at an arrow prompt (=>).

=> d ibib 1-3

L25 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:888105 CAPLUS

DOCUMENT NUMBER: 142:2821

TITLE: Dead cells in melanoma tumors  
provide abundant antigen for targeted delivery of  
ionizing radiation by a mAb to melanin

AUTHOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li;  
Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk,  
Jerome S.; Casadevall, Arturo

CORPORATE SOURCE: Department of Nuclear Medicine, Albert Einstein  
College of Medicine, Bronx, NY, 10461, USA

SOURCE: Proceedings of the National Academy of Sciences of the  
United States of America (2004), 101(41), 14865-14870  
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English



REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:654728 CAPLUS  
DOCUMENT NUMBER: 141:186978  
TITLE: Radiolabeled antibodies for treatment of tumors  
INVENTOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Casadevall, Arturo  
PATENT ASSIGNEE(S): USA  
SOURCE: U.S. Pat. Appl. Publ., 23 pp.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004156780	A1	20040812	US 2004-775869	20040210
PRIORITY APPLN. INFO.:			US 2003-446684P	P 20030211

L25 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:465553 CAPLUS  
DOCUMENT NUMBER: 115:65553  
TITLE: Mammalian melanin-concentrating hormones (MCHs) and methods of treatment using same  
INVENTOR(S): Vaughan, Joan; Fischer, Wolfgang Hermann; Rivier, Jean Edouard; Nahon, Jean Louis Marie; Presse, Francoise Genevieve; Vale, Wylie Walker, Jr.  
PATENT ASSIGNEE(S): Salk Institute for Biological Studies, USA  
SOURCE: PCT Int. Appl., 47 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9011295	A1	19901004	WO 1990-US1492	19900320
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
US 5049655	A	19910917	US 1989-326984	19890322
CA 2046900	AA	19900923	CA 1990-2046900	19900320
CA 2046900	C	20000822		
EP 464105	A1	19920108	EP 1990-905279	19900320
EP 464105	B1	19960814		
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
JP 04503812	T2	19920709	JP 1990-505271	19900320
JP 2944202	B2	19990830		
AT 141288	E	19960815	AT 1990-905279	19900320
US 5449766	A	19950912	US 1994-208531	19940309
US 5530095	A	19960625	US 1995-447613	19950523
PRIORITY APPLN. INFO.:			US 1989-326984	A 19890322
			WO 1990-US1492	W 19900320
			US 1991-733660	B3 19910722
			US 1994-208531	A3 19940309
OTHER SOURCE(S):		MARPAT 115:65553		

=> d kwic 3

L25 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

AB . . . characterized. The MCH and related peptides, formed from MCH precursors, are useful for treating skin disorders, suppressing proliferation of skin tumor (e.g. melanoma) cells in mammals, and modulating ACTH secretion. Also disclosed are the amino acid sequences and cDNA nucleotide sequences of rat. . .

ST rat melanin concg hormone; human melanin concg hormone; ACTH generation melanin concg hormone; skin neoplasm melanin cong hormone

IT Antibodies  
 RL: PROC (Process)  
 (to melanin-concentrating hormone of salmon, production of, for rat melanin-concentrating hormone purification)

IT Globins  
 RL: BIOL (Biological study)  
 ( $\alpha$ -subunits, conjugates, with melanin-concentrating hormone of salmon, for antibody production for rat melanin-concentrating hormone purification)

IT Proteins, specific or class  
 RL: BIOL (Biological study)  
 (A, conjugates, with Sepharose CL-4B and anti-salmon melanin-concentrating hormone antibody, for rat melanin-concentrating hormone purification)

IT 87218-84-6D, Melanin-concentrating hormone (Oncorhynchus keta),  $\alpha$ -globin conjugates  
 RL: BIOL (Biological study)  
 (for antibody production for rat melanin-concentrating hormone purification)

IT 61970-08-9D, Sepharose CL-4B, conjugates with protein A and anti-salmon melanin-concentrating hormone antibodies  
 RL: BIOL (Biological study)  
 (in rat melanin-concentrating hormone purification)

=> file pctfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	61.54	63.65
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.25	-2.25

FILE 'PCTFULL' ENTERED AT 14:16:40 ON 23 JAN 2006  
 COPYRIGHT (C) 2006 Univentio

FILE LAST UPDATED: 3 JAN 2006 <20060103/UP>  
 MOST RECENT UPDATE WEEK: 200552 <200552/EW>  
 FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> UPDATING DELAYED DUE TO DELIVERY FORMAT CHANGES. <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOT YET AVAILABLE IN THIS FILE.  
 USE IPC7 FORMAT FOR SEARCHING THE IPC. WATCH THIS SPACE FOR FURTHER DEVELOPMENTS AND SEE OUR NEWS SECTION FOR FURTHER INFORMATION ABOUT THE IPC REFORM <<<

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006

L1 9970 S MELANIN  
 L2 61483 S MELANOMA

L3 2328 S L2 AND L1  
L4 705098 S ANTIBOD?  
L5 198 S L3 AND L4  
L6 7 S ANTI (2W) MELANIN  
L7 2 S L6 AND L2  
L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006

L9 11188 S MELANIN  
L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?  
L11 1762 S L9 (L) L10  
L12 451938 S ANTIBOD?  
L13 60 S L11 AND L12  
L14 190 S L9 (L) L12  
L15 59 S L14 AND L10  
L16 53 S L14 AND L13  
L17 45 S L16 NOT PY>2002  
L18 413661 S IN VIVO  
L19 3 S L18 AND L17  
L20 4 S L17 AND LABEL?  
L21 46 S 6D2  
L22 2 S L21 AND L10  
L23 14 S ANTI (2W) MELANIN  
L24 7 S L23 AND ANTIBOD?  
L25 3 S L24 AND L10

FILE 'PCTFULL' ENTERED AT 14:16:40 ON 23 JAN 2006

=> s anti (2w) melanin  
167501 ANTI  
165 ANTIS  
167532 ANTI  
(ANTI OR ANTIS)  
2796 MELANIN  
190 MELANINS  
2854 MELANIN  
(MELANIN OR MELANINS)

L26 6 ANTI (2W) MELANIN

=> s l26 and antibod?  
84196 ANTIBOD?  
L27 1 L26 AND ANTIBOD?

=> d ibib

L27 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN  
ACCESSION NUMBER: 2004048547 PCTFULL ED 20040615 EW 200424  
TITLE (ENGLISH): INTERMEDIN AND ITS USES  
TITLE (FRENCH): INTERMEDINE ET SES UTILISATIONS  
INVENTOR(S): HSU, Sheau, Yu Teddy, 2038 Santa Cruz Avenue, Menlo  
Park, CA 94025, US  
PATENT ASSIGNEE(S): THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR  
UNIVERSITY, 1705 El Camino Real, Palo Alto, CA  
94306-1106, US [US, US]  
AGENT: SHERWOOD, Pamela J.\$, BOZICEVIC, FIELD & FRANCIS LLP,  
200 Middlefield Road, Suite 200, Menlo Park, CA 94025\$,  
US  
LANGUAGE OF FILING: English  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004048547	A2	20040610

## DESIGNATED STATES

W: AU CA JP  
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
MC NL PT RO SE SI SK TR  
APPLICATION INFO.: WO 2003-US37968 A 20031126  
PRIORITY INFO.: US 2002-60/429,327 20021126

=> s l26 and (cancer? or tumor? or neoplas?

UNMATCHED LEFT PARENTHESIS 'AND (CANCER?'

The number of right parentheses in a query must be equal to the number of left parentheses.

=> s l26 and (cancer? or tumor? or neoplas?)

74539 CANCER?

62442 TUMOR?

21534 NEOPLAS?

L28 3 L26 AND (CANCER? OR TUMOR? OR NEOPLAS?)

=> d ibib 1-3

L28 ANSWER 1 OF 3

ACCESSION NUMBER:

TITLE (ENGLISH):

TITLE (FRENCH):

INVENTOR(S):

PATENT ASSIGNEE(S):

PCTFULL COPYRIGHT 2006 Univentio on STN  
2004087128 PCTFULL ED 20041019 EW 200442  
METHYL-&Beta;-ORCINOLCARBOXYLATE FROM LICHEN  
(EVERNIASTRUM CIRRHATUM) FOR USE FOR THE TREATMENT OF  
FUNGAL INFECTIONS AND CANCER  
METHYL-BETA-ORCINOL-CARBOXYLATE TIRE DU LICHEN  
EVERNIASTRUM CIRRHATUM DESTINE AU TRAITEMENT  
D'INFECTIONS FONGIQUES ET DU CANCER  
KHANUJA, Suman, Preet, Singh, Central Institute Of  
Medicinal And Aromatic Plants, P.O. CIMAP, Lucknow 226  
015, Uttar Pradesh, IN;  
TIRUPPADIRIPULIYUR, Ranganathan, Santha, Kumar, Central  
Institute of Medicinal and Aromatic Plants, P.O. CIMAP,  
Lucknow 226 015, Uttar Pradesh, IN;  
GUPTA, Vivek, Kumar, Central Institute of Medicinal and  
Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar  
Pradesh, IN;  
CHAND, Preeti, Central Institute of Medicinal and  
Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar  
Pradesh, IN;  
GARG, Ankur, Central Institute of Medicinal and  
Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar  
Pradesh, IN;  
SRIVASTAVA, Santosh, Kumar, Central Institute of  
Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226  
015, Uttar Pradesh, IN;  
VERMA, Subash, Chandra, Central Institute of Medicinal  
and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar  
Pradesh, IN;  
SAIKIA, Dharmendra, Central Institute of Medicinal and  
Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar  
Pradesh, IN;  
DAROKAR, Mahendra, Pandurang, Central Institute of  
Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226  
015, Uttar Pradesh, IN;  
SHASANY, Ajit, Kumar, Central Institute of Medicinal  
and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar  
Pradesh, IN;  
PAL, Anirban, Central Institute of Medicinal and  
Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar  
Pradesh, IN  
COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, Rafi  
Marg, New Delhi 110 001, IN [IN, IN]

AGENT: SUBRAMANIAM, Hariharan\$, Subramaniam, Nataraj & Associates, E-556 Greater Kailash II, New Delhi 110 048\$, IN  
LANGUAGE OF FILING: English  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004087128	A1	20041014

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR  
CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID  
IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD  
MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SK  
SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

RW (ARIPO):

GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

RW (EAPO):

AM AZ BY KG KZ MD RU TJ TM

RW (EPO):

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
MC NL PT RO SE SI SK TR

RW (OAPI):

BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.:

WO 2003-IN97 A 20030331

L28 ANSWER 2 OF 3

ACCESSION NUMBER:

PCTFULL COPYRIGHT 2006 Univentio on STN

TITLE (ENGLISH):

2004048547 PCTFULL ED 20040615 EW 200424

TITLE (FRENCH):

INTERMEDIN AND ITS USES

INVENTOR(S):

INTERMEDINE ET SES UTILISATIONS

HSU, Sheau, Yu Teddy, 2038 Santa Cruz Avenue, Menlo Park, CA 94025, US

PATENT ASSIGNEE(S):

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AGENT:

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LANGUAGE OF FILING:

English

LANGUAGE OF PUBL.:

English

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004048547	A2	20040610

DESIGNATED STATES

W:

AU CA JP

RW (EPO):

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
MC NL PT RO SE SI SK TR

APPLICATION INFO.:

WO 2003-US37968 A 20031126

PRIORITY INFO.:

US 2002-60/429,327 20021126

L28 ANSWER 3 OF 3

ACCESSION NUMBER:

PCTFULL COPYRIGHT 2006 Univentio on STN

TITLE (ENGLISH):

2003035167 PCTFULL ED 20030512 EW 200318

TITLE (FRENCH):

DEVICE AND METHOD FOR CONTROLLED DELIVERY OF ACTIVE SUBSTANCE INTO THE SKIN

DISPOSITIF ET PROCEDE DE LIBERATION CONTROLEE D'UNE SUBSTANCE ACTIVE DANS LA PEAU

INVENTOR(S):

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 MAVOR, Daniela, 36 Striker Street, 62006 Tel Aviv, IL  
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 TAMARKIN, Dov, 537 Har Hila Street, 91708 Maccabim, IL  
 [IL, IL], for US only;  
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 IL [IL, IL], for US only;  
 HAREL, Nurit, 5 Benayahu Street, 69084 Tel Aviv, IL  
 [IL, IL], for US only;  
 GROSS, Yossi, Moshav Mazor 205, 73160 Moshav Mazor, IL  
 [IL, IL], for US only  
 AGENT: REINHOLD COHN AND PARTNERS\$, P.O.B. 4060, 61040 Tel  
 Aviv\$, IL  
 LANGUAGE OF FILING: English  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2003035167	A2	20030501

DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR  
 CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID  
 IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD  
 MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI  
 SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW  
 RW (EAPO): AM AZ BY KG KZ MD RU TJ TM  
 RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC  
 NL PT SE SK TR  
 RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-IL849 A 20021023  
 PRIORITY INFO.: US 2001-60/330,526 20011024  
 US 2002-60/401,771 20020808

=> s WO 199011295/pn  
 L29 1 WO 199011295/PN  
 (WO9011295/PN)

=> s melanin and 129  
 2796 MELANIN  
 190 MELANINS  
 2854 MELANIN  
 (MELANIN OR MELANINS)  
 L30 1 MELANIN AND L29

=> s 130 and antibod?  
 84196 ANTIBOD?  
 L31 1 L30 AND ANTIBOD?

=> s cancer? or tumor? or neoplas?  
 74539 CANCER?  
 62442 TUMOR?  
 21534 NEOPLAS?  
 L32 93014 CANCER? OR TUMOR? OR NEOPLAS?

=> s 132 and 131

L33

1 L32 AND L31

=> d kwic

L33 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN  
TIEN MELANIN-CONCENTRATING HORMONES AND METHODS OF TREATMENT USING  
SAME

PI WO 9011295 A1 19901004

ABEN Mammalian melanin-concentrating hormone (MCH) is isolated from  
rat tissue, purified and  
characterized. These MCH peptides are useful for treating skin  
disorders, for suppressing the  
proliferation of skin tumor cells, such as melanomas in  
mammals, and for modulating the secretion of  
ACTH. Generally, peptides are provided which have formula. . . are  
thought to be formed from the MCH precursors, are the peptides with the  
sequence  
H-Glu-Ile-Gly-Asp-Glu-Glu-Asn-Ser-Ala-Lys-Phe-Pro-Ile-NH<sub>2</sub>, which is  
cross-reactive with antibodies  
against alpha-MSH and CRF, and the peptides with the sequence  
H-Gly-XNGE-Phe-Pro-Ala-Glu-Asn-Gly-Val-Gln-Asn-Thr-Glu-Ser-Thr-Gln-Glu-  
OH, wherein XNGE is  
Pro-Ala-Val or Ser-Val-Ala, which is cross-reactive with  
antibodies against GRF.

ABFR . . . caracterisee. Ces peptides de MCH sont utiles pour traiter des  
troubles de la  
peau, pour supprimer la proliferation de cellules tumorales de  
la peau, telles que les melanomes  
chez les mammiferes, et pour moduler la secretion de ACTH. En general,  
les. . .

DETD MELANIN-CONCENTRATING HORNONES  
AND METHODS OF TREATMMff USING SAME  
This invention relates to hormones for  
concentrating melanin in mammals and to methods of  
treating mammals using such hormones,  
BACKGROUND OF THE INVENTION  
A cyclic heptadecapeptide which induces  
melanosome aggregation within fish. . .

et al., Nature, 305, 321-323 (1983), and it was named  
melanin concentrating hormone (MCH). Fish MCH has been  
reported to have the opposite effect, i.e., causing  
dispersal of melanosomes, in amphibians, Wilkes, B.. . .

. . .  
mammals to lighten skin color, as by local or  
topical application. It is also useful to suppress the  
proliferation of certain skin tumor cells, such as  
melanomas, when suitably applied as by topical appli-  
cation or the like. It is also found that mammalian MCH  
can. . .

. . .  
at position 144 of the MCH  
precursors would provide the NH<sub>2</sub> group of the  
C-terminal amide of NEI. It has been found that  
antibodies against human alpha-MSH (i.e.,  
alpha[melanocyte stimulating hormone) and human CRF  
(corticotropin-releasing factor) cross]react with NEI,  
with the anti-alpha-MSH antibodies recognizing an epitope  
including the N-terminus of NEI and the anti-CRF  
antibodies recognizing an epitope including the  
C-terminus of NEI, It is thought that NEI has a  
biological function in vivo-,  
The sequences of the NGE's correspond to the

sequences of amino acids 110 - 128 of the MCH precursors (see Tables 1 and 2, below). Antibodies against human GRF (growth hormone releasing factor) crossreact with NGE, as suggested by our discovery of the close homology between the sequence Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu. . .

NEI is useful, in the process of making anti-alpha-MSH or anti-CRF monoclonal antibody-secreting hybridomas, as an immunogen for obtaining anti-alpha-MSH or anti-CRF antibody-producing splenocytes or lymphocytes and as an antigen for screening cultures of hybridomas for those which include hybridomas that make anti-MSH or anti-CRF antibodies. Similarly, NGE is useful in the process of making anti-GRF monoclonal antibody-secreting hybridomas. Monoclonal antibodies made by such hybridomas are useful for assaying for alpha-MSH, CRF or GRF by standard immunoassay methods.

Further, such a monoclonal antibody made with NEI or NGE as the immunogen, when used in a standard immunoassay procedure in conjunction with a second monoclonal antibody, which recognizes an epitope of alpha-MSH, CRF or GRF different from the epitope recognized by the monoclonal antibody made with NEI or NGE as the immunogen, can be used to confirm that a peptide detected in an immunoassay is alpha-MSH, . . . between NEI and alpha-MSH, NEI and CRF, or NGE and GRF. Such a confirmatory assay would be useful, for example, in assaying tumor cells, from a patient thought to be suffering from a cancer involving aberrant expression of alpha-MSH, CRF or GRF, to ascertain whether the cancer does in fact entail aberrant expression of one of those hormones or entails instead aberrant expression of NEI, NGE or some other. . .

#### DETAILED DESCRIPTION OF THE INVENTION

Mammalian melanin-concentrating hormone (MCH) has now been isolated from rat hypothalamus by acid extraction and purified substantially by immunoaffinity chromatography using antiserum directed against salmon MCH, . . .

color of a mammal comprising administering thereto an effective amount of such a MCH, a method of suppressing the proliferation of skin tumor cells in a mammal comprising administering thereto an effective amount of such a MCH, and a method of suppressing the secretion of ACTH. . .

through nucleic acid probe hybridization analysis clones containing MCH-encoding sequences. If the library is an expression library, screening of the library with anti-MCH antibodies (alone or together with anti-NEI or anti-NGE antibodies) may also be used, alone or in conjunction with nucleic acid probe hybridization probing, to identify or confirm the presence of MCH-encoding or. . .

Throughout the purification, fractions are monitored using an RIA based upon this rabbit anti-salmon MCH antibody. Aliquots for assay are transferred into glass tubes containing BSA (10  $\mu$ l of 10 mg/ml) and dried in a Savant Speed Vac. . . is carried out using chilled reagents and with tubes partially immersed in ice



water. On day one, 100 Al of buffer with Antibody PBL #171 1/24,000 dilution (1/120,000 final dilution) is added to glass tubes containing standard or test samples or buffer only in a volume. . . to all tubes. The tubes are vortexed and returned to the cold for approximately 24 hours. On day three, tracer bound to antibody is precipitated with sheep anti[rabbit gamma globulins (100 Ali 1/40 dilution) and 0.5 ml of 10%(w/v) polyethylene glycol (SIGMA, MW = 6,000 to. . .

supernatant removed, and the reaction stopped by resuspending the beads in 20 volumes (200 mls) of 0.02 M ethanolamine-Cl, pH 8 The antibody]Protein A beads are then washed twice with 1 N HAc and equilibrated with 50 mM Na HEPES, 150 mM NaCl, pH 7\*5e. . .

of the peptide for the topical application, and, in this respect, could rely upon data generated in connection with the use of MSH (melanin stimulating hormone) antagonists for this purpose.

CLMEN I. A cyclic mammalian hormone capable of concentrating mammalian melanin, which is a peptide with about 19 residues, or a physiologically acceptable salt of said mammalian hormone.  
2\* A mammalian hormone in accordance. . . which, if expressed, would yield a polypeptide with the amino acid sequence of a cyclic mammalian hormone, which is capable of concentrating mammalian melanin and is a peptide with about 19 residues, or, if said hormone is C]terminally amidated, said amino acid sequence with a Gly. . .

=> s antibod? same melanin  
84196 ANTIBOD?  
661070 SAME  
391 SAMES  
661322 SAME  
(SAME OR SAMES)  
2796 MELANIN  
190 MELANINS  
2854 MELANIN  
(MELANIN OR MELANINS)  
L34 0 ANTIBOD? SAME MELANIN  
(ANTIBOD? (W) SAME (W) MELANIN)

=> s antibod? (S) melanin  
84196 ANTIBOD?  
2796 MELANIN  
190 MELANINS  
2854 MELANIN  
(MELANIN OR MELANINS)  
L35 118 ANTIBOD? (S) MELANIN

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006

L1 9970 S MELANIN  
L2 61483 S MELANOMA  
L3 2328 S L2 AND L1  
L4 705098 S ANTIBOD?

L5 198 S L3 AND L4  
 L6 7 S ANTI (2W) MELANIN  
 L7 2 S L6 AND L2  
 L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006

L9 11188 S MELANIN  
 L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?  
 L11 1762 S L9 (L) L10  
 L12 451938 S ANTIBOD?  
 L13 60 S L11 AND L12  
 L14 190 S L9 (L) L12  
 L15 59 S L14 AND L10  
 L16 53 S L14 AND L13  
 L17 45 S L16 NOT PY>2002  
 L18 413661 S IN VIVO  
 L19 3 S L18 AND L17  
 L20 4 S L17 AND LABEL?  
 L21 46 S 6D2  
 L22 2 S L21 AND L10  
 L23 14 S ANTI (2W) MELANIN  
 L24 7 S L23 AND ANTIBOD?  
 L25 3 S L24 AND L10

FILE 'PCTFULL' ENTERED AT 14:16:40 ON 23 JAN 2006

L26 6 S ANTI (2W) MELANIN  
 L27 1 S L26 AND ANTIBOD?  
 L28 3 S L26 AND (CANCER? OR TUMOR? OR NEOPLAS?)  
 L29 1 S WO 199011295/PN  
 L30 1 S MELANIN AND L29  
 L31 1 S L30 AND ANTIBOD?  
 L32 93014 S CANCER? OR TUMOR? OR NEOPLAS?  
 L33 1 S L32 AND L31  
 L34 0 S ANTIBOD? SAME MELANIN  
 L35 118 S ANTIBOD? (S) MELANIN

=> s 132 and 135

L36 106 L32 AND L35

=> s melanin/ab

214 MELANIN/AB  
 9 MELANINS/AB  
 L37 217 MELANIN/AB  
 ((MELANIN OR MELANINS)/AB)

=> s melanin/ti

100 MELANIN/TI  
 6 MELANINS/TI  
 L38 106 MELANIN/TI  
 ((MELANIN OR MELANINS)/TI)

=> s 138 or 137

L39 239 L38 OR L37

=> s 139 and 136

L40 12 L39 AND L36

=> d ibib 1-6

L40 ANSWER 1 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN  
 ACCESSION NUMBER: 2004093518 PCTFULL ED 20041110 EW 200445  
 TITLE (ENGLISH): IMMUNOSTIMULATORY AGENTS IN BOTANICALS  
 TITLE (FRENCH): AGENTS IMMUNOSTIMULATEURS PRESENTS DANS DES PRODUITS  
 PHYTOPHARMACEUTIQUES

INVENTOR(S): PASCO, David S, 706 Oakhill Drive, Oxford, MS 38655, US [US, US];  
PUGH, Nirmal, D, 401 Thacker Loop, Oxford, MS 38655, US [US, US];  
KHAN, Ikhlas, A, Shelia Drive 65, Oxford, MS 38655, US [US, US];  
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PATENT ASSIGNEE(S): THE UNIVERSITY OF MISSISSIPPI, 125 Old Chemistry, University, MS 38677, US [US, US], for all designates States except US;  
PASCO, David S, 706 Oakhill Drive, Oxford, MS 38655, US [US, US], for US only;  
PUGH, Nirmal, D, 401 Thacker Loop, Oxford, MS 38655, US [US, US], for US only;  
KHAN, Ikhlas, A, Shelia Drive 65, Oxford, MS 38655, US [US, US], for US only;  
MORAES, Rita, 307 Deer Run, Oxford, MS 38655, US [US, US], for US only

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LANGUAGE OF FILING: English  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 2004093518	A2	20041104
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DESIGNATED STATES

W:

AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO  
CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR  
HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO  
RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ  
VC VN YU ZA ZM ZW

RW (ARIPO):

BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

RW (EAPO):

AM AZ BY KG KZ MD RU TJ TM

RW (EPO):

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU  
MC NL PL PT RO SE SI SK TR

RW (OAPI):

BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.:

WO 2004-US11886	A	20040416
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PRIORITY INFO.:

US 2003-60/463,169		20030416
US 2004-60/538,676		20040123

L40 ANSWER 2 OF 12

ACCESSION NUMBER:

PCTFULL COPYRIGHT 2006 Univentio on STN

2002008290 PCTFULL ED 20020814

TITLE (ENGLISH):

DOG MELANIN-CONCENTRATING HORMONE RECEPTOR

TITLE (FRENCH):

RECEPTEUR DE L'HORMONE CONCENTRANT LA MELANINE DU CHIEN

INVENTOR(S):

TAN, Carina, P.

PATENT ASSIGNEE(S):

MERCK &CO., INC.;

TAN, Carina, P.

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 2002008290	A1	20020131
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DESIGNATED STATES

W:

CA JP US AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC  
NL PT SE TR

APPLICATION INFO.:

WO 2001-US22458	A	20010717
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PRIORITY INFO.:

US 2000-60/219,669		20000721
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L40 ANSWER 3 OF 12

ACCESSION NUMBER:

PCTFULL COPYRIGHT 2006 Univentio on STN

2001098464 PCTFULL ED 20020826

TITLE (ENGLISH): CONTINUOUS ADHERENT MELANOCYTE CELL LINE  
 TITLE (FRENCH): LIGNEE CELLULAIRE ADHERENTE CONTINUE DE MELANOCYTE  
 INVENTOR(S): ALEXANDER, Jeannine;  
 COX, William, I.  
 PATENT ASSIGNEE(S): AVENTIS PASTEUR LIMITED;  
 ALEXANDER, Jeannine;  
 COX, William, I.  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001098464	A2	20011227

DESIGNATED STATES  
 W:

AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU  
 CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN  
 IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK  
 MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM  
 TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD  
 SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY  
 DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF  
 CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US40540 A 20010418  
 PRIORITY INFO.: US 2000-60/213,613 20000622

L40 ANSWER 4 OF 12  
 ACCESSION NUMBER:  
 TITLE (ENGLISH):

PCTFULL COPYRIGHT 2006 Univentio on STN  
 2000010507 PCTFULL ED 20020515  
 USE OF MELANIN FOR INHIBITION OF ANGIOGENESIS  
 AND MACULAR DEGENERATION

TITLE (FRENCH):

UTILISATION DE MELANINE POUR INHIBER L'ANGIOGENESE ET  
 LA DEGENERESCENCE MACULAIRE

INVENTOR(S):  
 PATENT ASSIGNEE(S):

D'AMATO, Robert, J.  
 THE CHILDREN'S MEDICAL CENTER CORPORATION;  
 D'AMATO, Robert, J.

LANGUAGE OF PUBL.:  
 DOCUMENT TYPE:  
 PATENT INFORMATION:

English  
 Patent

NUMBER	KIND	DATE
WO 2000010507	A2	20000302

DESIGNATED STATES  
 W:

AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE  
 DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE  
 KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO  
 NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US  
 UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY  
 KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE  
 IT LU MC NL PT SE

APPLICATION INFO.: WO 1999-US19026 A 19990820  
 PRIORITY INFO.: US 1998-60/097,385 19980821

L40 ANSWER 5 OF 12  
 ACCESSION NUMBER:  
 TITLE (ENGLISH):

PCTFULL COPYRIGHT 2006 Univentio on STN  
 1999006074 PCTFULL ED 20020515  
 USE OF TEXAPHYRINS IN DETECTION OF MELANIN  
 AND MELANIN METABOLITES OF MELANOTIC MELANOMA  
 UTILISATION DE TEXAPHYRINES DANS LA DETECTION DE LA  
 MELANINE ET DES METABOLITES DE LA MELANINE DU MELANOME  
 MELANIQUE

INVENTOR(S):  
 PATENT ASSIGNEE(S):

WOODBURN, Kathryn, W.;  
 YOUNG, Stuart, W.  
 PHARMACYCLICS, INC.;  
 WOODBURN, Kathryn, W.;  
 YOUNG, Stuart, W.

LANGUAGE OF PUBL.:  
 DOCUMENT TYPE:

English  
 Patent

## PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9906074	A1	19990211
DESIGNATED STATES			
W:	AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 1998-US15833	A	19980729
PRIORITY INFO.:	US 1997-08/903,099		19970730

L40 ANSWER 6 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN  
 ACCESSION NUMBER: 1998034602 PCTFULL ED 20020514  
 TITLE (ENGLISH): MEDIATION OF CYTOKINES BY MELANIN  
 TITLE (FRENCH): REGULATION DE LA PRODUCTION DE CYTOKINES PAR LA  
 MELANINE  
 INVENTOR(S): MOHAGHEGHPOUR, Nahid  
 PATENT ASSIGNEE(S): BIOSOURCE TECHNOLOGIES, INC.  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9834602	A2	19980813
DESIGNATED STATES			
W:	AU BG CA IL JP KR MX AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1998-US2971	A	19980210
PRIORITY INFO.:	US 1997-8/798,846		19970212

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L40 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN  
 TIEN USE OF MELANIN FOR INHIBITION OF ANGIOGENESIS AND MACULAR  
 DEGENERATION  
 ABEN Compositions and methods of using melanin, or melanin  
 -promoting compounds, for inhibiting  
 angiogenesis to treat angiogenesis-dependent diseases, such as macular  
 degeneration and cancer.  
 ABFR . . . de melanine permettant d'inhiber l'angiogenese afin de traiter  
 les maladies dependantes  
 de l'angiogenese telles que la degenerescence maculaire et le  
 cancer.  
 DETD . . . ANGIOGENESIS  
 AND MACULAR DEGENERATION  
 Technical Field  
 This application relates to an inhibitor of ancriogenesis useful  
 for treating angiogenesis-related diseases, such as macular degeneration  
 and  
 angiogenesis-dependent cancers. The invention further relates  
 to novel  
 pharmaceutical compositions and methods for treating and curing macular  
 degeneration, and other angiogenesis-dependent diseases.  
 Persistent, unregulated angiogenesis occurs in a multiplicity of  
 disease states, tumor metastasis and abnormal growth by  
 endothelial cells  
 and supports the pathological damage seen in these conditions. The

diverse  
pathological states created due. . .

One of the most frequent angiogenic diseases of childhood is the hemangioma. In most cases, the tumors are benign and regress without intervention. In more severe cases, the tumors progress to large cavernous and infiltrative forms and create clinical complications. Systemic forms of hemangiomas, the hemangiomatoses, have a high mortality rate.

damage found in hereditary

9

diseases such as Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small angiomas, tumors of blood or lymph vessels. The angiomas are found in the skin and mucous membranes, often accompanied by epistaxis (nosebleeds) or gastrointestinal. . .

Angiogenesis is prominent in solid tumor formation and metastasis. Several lines of direct evidence now suggest that angiogenesis is essential for the growth and persistence of solid tumors and their metastases (Folkman, 1989; Hori et al., 1991; Kim et al., 1993; Millauer et al., 1994).

To stimulate angiogenesis, tumors upregulate their production of a variety of angiogenic factors, including the fibroblast growth factors (FGF and bFGF) (Kandel et al., 1991) and vascular endothelial cell growth factor/vascular permeability factor (VEGF/VPF). However, many malignant tumors also generate inhibitors of angiogenesis, including angiostatin and thrombospondin (Chen et al., 1995; Good et al., 1990; O'Reilly et al., 1994).

et al., 1989). Several other endogenous inhibitors of angiogenesis have been identified, although not all are associated with the presence of a tumor.

Melanin pigments play a critical role in the development of skin cancers such as melanoma, which involves tumor development from transformed melanocytes. Light-skinned individuals with more pheomelanin tend to have a higher incidence of melanoma than darker skinned individuals, perhaps due. . .

melanomas. This teaches away the current invention in which increased levels of melanin are disclosed to decrease angiogenesis (blood vessel formation in tumors) and thus lead to decreased tumor size and formation.

for treating or for repressing macular degeneration. Administration of melanin, or a melanin-promoting compound to a human or animal with prevascularized metastasized tumors

prevents the growth or expansion of those tumors.

The present invention also includes diagnostic methods and kits for detection and measurement of melanin, or a melanin-promoting compound, in biological fluids and tissues, and for localization of melanin, or a melanin-promoting compound, in tissues. The diagnostic method and kit can be in any configuration well known to those of ordinary skill in the art. The present invention also includes antibodies specific for the melanin, or a melanin-promoting compound, and antibodies that inhibit the binding of antibodies specific for the melanin, or a melanin-promoting compound.

The antibodies specific for melanin, or a melanin-promoting compound, can be used in diagnostic kits to detect the presence and quantity of melanin, or a melanin-promoting compound, which is diagnostic or prognostic for the occurrence or recurrence of cancer or other disease mediated by angiogenesis. Antibodies specific for melanin, or a melanin-promoting compound, may also be administered to a human or animal to passively immunize the human or animal against melanin, or a melanin-promoting compound, thereby reducing angiogenic inhibition.

The present invention also relates to methods of using the melanin, or a melanin-promoting compound, fragments, and antibodies that bind specifically to the inhibitor and its fragments, to diagnose endothelial cell-related diseases and disorders.

that are mediated by angiogenesis including, but not limited to macular degeneration, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, hemangioma, solid tumors, leukernia, metastasis, telanglectasia psoriasis scleroderma, pyogenic granuloma, - 10 - myocardial anglogenesis, plaque neovascularization, corornay collaterals, cerebral collaterals, arteriovenous malformations, ischernic limb angiogenesis, arthritis, diabetic. . .

It is another object of the present invention to provide a composition for treating or repressing the growth of a cancer.

It is an object of present invention to provide a method for detecting and quantifying the presence of an antibody specific for an melanin, or a melanin-promoting compound, in a body fluid.

Still another object of the present invention is to provide a composition consisting of antibodies to melanin, or a melanin-promoting

compound, that are selective for specific regions of the melanin  
, or a  
melanin-promoting compound, molecule.

It is another object of the present invention to provide a method  
for the detection or prognosis of cancer.

Still another object of the present invention is to provide a  
composition comprising melanin, or a melanin-promoting compound, linked  
to a cytotoxic agent for treating or repressing the growth of a  
cancer.

inhibiting  
angiogenesis are melanin and melanin-promoting compounds. The inhibitor  
compounds of the invention are useful for treating angiogenesis-related  
diseases, particularly macular degeneration, and angiogenesis-dependent  
cancers and tumors. The unexpected and surprising  
ability of melanin to  
treat and cure angiogenesis-dependent diseases answers a long felt and  
unfulfilled need in the. . .

inhibiting activity include the chick CAM assay,  
the mouse corneal assay, and the effect of administering isolated or  
synthesized proteins on implanted tumors. The chick CAM assay  
is  
described by O'Reilly, et al. in Angiogenic Regulation of Metastatic  
Growth Cell, vol. 79 (2), October 21, . . .

Cancer means angiogenesis-dependent cancers and  
tumors, i.e. tumors that  
require for their growth (expansion in volume and/or mass) an increase  
in  
the number and density of the blood vessels supplying. . .

Regression refers to the reduction of tumor mass and size.

melanin, or  
a melanin-promoting compound, in body fluids and tissues for the purpose  
of diagnosis or prognosis of angiogenesis-mediated diseases such as  
cancer.

tissues. The  
present invention also includes methods of treating or preventing  
angiogenic  
diseases and processes including, but not limited to, macular  
degeneration  
and tumors by stimulating the production of melanin, and/or by  
administering substantially purified melanin, or a melanin-associated  
compound, or a fusion protein containing the. . .

Passive antibody therapy using antibodies that  
specifically bind  
melanin can be employed to modulate endothelial-dependent  
processes such  
as reproduction, development, and wound healing and tissue repair.

Antibodies specific for melanin, or a  
melanin-promoting compound, are  
made according to techniques and protocols well-known in the art. The  
- 13 -

antibodies may be either polyclonal or monoclonal. The  
antibodies are  
utilized in well-know immunoassay formats, such as competitive and non-  
competitive immunoassays, including ELISA, sandwich immunoassays and



radioimmunoassays (RIAs), to determine the. . .

. . .  
limited to,  
ocular angiogenic diseases, for example, diabetic retinopathy,  
retinopathy of  
prematurity, macular degeneration, corneal graft rejection, neovascular  
glaucoma, retrolental fibroplasia, rubeosis; angiogenesis-dependent  
cancer,  
including, for example, solid tumors, blood born  
tumors such as leukemias,  
and tumor metastases; benign tumors, for example  
hemangiomas, acoustic  
neuromas, neurofibromas, trachomas, and pyogenic granulomas; rheumatoid  
arthritis; psoriasis; Osler-Webber Syndrome; myocardial angiogenesis;  
plaque neovascularization; telangiectasia; hemophiliac joints;  
angiofibroma;  
and. . .

. . .  
cardiac muscle  
especially following transplantation of a heart or heart tissue and  
after  
bypass surgery, promotion of vascularization of solid and relatively  
avascular tumors for enhanced cytotoxin delivery, and  
enhancement of  
blood flow to the nervous system, including but not limited to the  
cerebral  
cortex and. . .

. . .  
destruction of cells that bind melanin. These cells may  
be found in many locations, including but not limited to,  
micrometastases  
and primary tumors. Peptides linked to cytotoxic agents are  
infused in a  
manner designed to maximize delivery to the desired location. For  
example,  
ricin-linked high. . . antagonists may be co-applied  
with stimulators of angiogenesis to increase vascularization of tissue.  
This  
therapeutic regimen provides an effective means of destroying metastatic  
cancer.

. . .  
a melanin-  
promoting compound, may be used in combination with other compositions  
and procedures for the treatment of diseases. For example, a  
tumor may be  
treated conventionally with surgery, radiation or chemotherapy combined  
with melanin, and then another anti-angiogenic compound may be  
subsequently administered to the patient to extend the dormancy of  
micrometastases and to stabilize any residual primary tumor.

. . .  
the compound, the  
polymers being implanted in the vicinity of where drug delivery is  
desired,  
for example, at the site of a tumor or implanted so that the  
endostatin is  
slowly released systemically. Osmotic minipumps may also be used to  
provide controlled delivery of high. . . through cannulae to the site  
of interest, such as  
directly into a metastatic growth or into the vascular supply to that  
tumor.

Kits for measurement of melanin, or a melanin  
-promoting  
compound, are also contemplated as part of the present invention.

Antisera

that possess the highest titer and specificity and can detect the . . .  
and non-competitive assays,  
radioimmunoassay, bioluminescence and chemiluminescence assays,  
fluorometric assays, sandwich assays, immunoradiometric assays, dot  
blots,  
enzyme linked assays including ELISA, microtiter plates,  
antibody coated

- 18 -

strips or dipsticks for rapid monitoring of urine or blood, and  
immunocytochemistry. For each kit the range, sensitivity, precision,  
reliability, . . .

. . .  
in the pigmented layer of the eye,  
or choroid, compared to white patients. Additionally, black patients  
have a  
reduced incidence of vascular tumors in the skin such as  
childhood  
hemangiomas. However, there are other inherent racial differences  
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white and black individuals besides pigmentation, and. . .

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L40 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN  
ACCESSION NUMBER: 2000010507 PCTFULL ED 20020515  
TITLE (ENGLISH): USE OF MELANIN FOR INHIBITION OF ANGIOGENESIS  
AND MACULAR DEGENERATION  
TITLE (FRENCH): UTILISATION DE MELANINE POUR INHIBER L'ANGIOGENESE ET  
LA DEGENERESCENCE MACULAIRE  
INVENTOR(S): D'AMATO, Robert, J.  
PATENT ASSIGNEE(S): THE CHILDREN'S MEDICAL CENTER CORPORATION;  
D'AMATO, Robert, J.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 2000010507	A2	20000302

DESIGNATED STATES

W:

AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE  
DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE  
KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO  
NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US  
UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY  
KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE  
IT LU MC NL PT SE

APPLICATION INFO.: WO 1999-US19026 A 19990820

PRIORITY INFO.: US 1998-60/097,385 19980821

TIEN USE OF MELANIN FOR INHIBITION OF ANGIOGENESIS AND MACULAR  
DEGENERATION

ABEN Compositions and methods of using melanin, or melanin  
-promoting compounds, for inhibiting  
angiogenesis to treat angiogenesis-dependent diseases, such as macular  
degeneration and cancer.

ABFR . . . de melanine permettant d'inhiber l'angiogenese afin de traiter  
les maladies dependantes  
de l'angiogenese telles que la degenerescence maculaire et le  
cancer.

DETD . . . ANGIOGENESIS  
AND MACULAR DEGENERATION  
Technical Field

This application relates to an inhibitor of angiogenesis useful  
for treating angiogenesis-related diseases, such as macular degeneration  
and  
angiogenesis-dependent cancers. The invention further relates  
to novel  
pharmaceutical compositions and methods for treating and curing macular  
degeneration, and other angiogenesis-dependent diseases.

Persistent, unregulated angiogenesis occurs in a multiplicity of  
disease states, tumor metastasis and abnormal growth by  
endothelial cells  
and supports the pathological damage seen in these conditions. The  
diverse  
pathological states created due. . .

One of the most frequent angiogenic diseases of childhood is  
the hemangioma. In most cases, the tumors are benign and  
regress without  
intervention. In more severe cases, the tumors progress to  
large cavernous  
and infiltrative forms and create clinical complications. Systemic forms  
of

hemangiomas, the hemangiomatoses, have a high mortality rate.

damage found in hereditary

9

diseases such as Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small

angiomas, tumors of blood or lymph vessels. The angiomas are found in the

skin and mucous membranes, often accompanied by epistaxis (nosebleeds) or gastrointestinal. . .

Angiogenesis is prominent in solid tumor formation and metastasis. Several lines of direct evidence now suggest that angiogenesis is

essential for the growth and persistence of solid tumors and their metastases

(Folkman, 1989; Hori et al., 1991; Kim et al., 1993; Millauer et al., 1994).

To stimulate angiogenesis, tumors upregulate their production of a variety of

angiogenic factors, including the fibroblast growth factors (FGF and bFGF)

(Kandel et al., 1991) and vascular endothelial cell growth factor/vascular

permeability factor (VEGF/VPF). However, many malignant tumors also

generate inhibitors of angiogenesis, including angiostatin and thrombospondin (Chen et al., 1995; Good et al., 1990; O'Reilly et al., 1994).

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1989). Several other endogenous inhibitors of angiogenesis have been identified, although not all are associated with the presence of a tumor.

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cancers such as melanoma, which involves tumor development from

transformed melanocytes. Light-skinned individuals with more pheomelanin tend to have a higher incidence of melanoma than darker skinned individuals, perhaps due. . .

melanomas. This teaches away the current

invention in which increased levels of melanin are disclosed to decrease angiogenesis (blood vessel formation in tumors) and thus lead to decreased

tumor size and formation.

for treating or for repressing macular

degeneration. Administration of melanin, or a melanin-promoting compound to a human or animal with prevascularized metastasized tumors

prevents the growth or expansion of those tumors.

The present invention also includes diagnostic methods and kits for detection and measurement of melanin, or a melanin-promoting

compound, in biological fluids and tissues, and for localization of melanin,

or a melanin-promoting compound, in tissues. The diagnostic method and

kit can be in any configuration well known to those of ordinary skill in

the  
art. The present invention also includes antibodies specific  
for the melanin,  
or a melanin-promoting compound, and antibodies that  
inhibit the binding of  
antibodies specific for the melanin, or a  
melanin-promoting compound.

The antibodies specific for melanin, or a  
melanin-promoting compound, can  
be used in diagnostic kits to detect the presence and quantity of  
melanin, or a  
melanin-promoting compound, which is diagnostic or prognostic  
for the  
occurrence or recurrence of cancer or other disease mediated  
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compound, may also be administered to a human or animal to passively  
immunize the human or animal against melanin, or a  
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The present invention also relates to methods of using the  
melanin, or a melanin-promoting compound, fragments,  
and antibodies that  
bind specifically to the inhibitor and its fragments, to diagnose  
endothelial  
cell-related diseases and disorders.

that are  
mediated by angiogenesis including, but not limited to macular  
degeneration, corneal diseases, rubeosis, neovascular glaucoma, diabetic  
retinopathy, retrolental fibroplasia, hemangioma, solid tumors  
, leukernia,  
metastasis, telanglectasia psoriasis scleroderma, pyogenic granuloma,  
- 10 -  
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collaterals,  
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It is another object of the present invention to provide a  
composition for treating or repressing the growth of a cancer.

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composition consisting of antibodies to melanin, or  
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It is another object of the present invention to provide a method  
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Still another object of the present invention is to provide a  
composition comprising melanin, or a melanin-promoting compound, linked  
to a cytotoxic agent for treating or repressing the growth of a

cancer.

inhibiting

angiogenesis are melanin and melanin-promoting compounds. The inhibitor compounds of the invention are useful for treating angiogenesis-related diseases, particularly macular degeneration, and angiogenesis-dependent cancers and tumors. The unexpected and surprising ability of melanin to treat and cure angiogenesis-dependent diseases answers a long felt and unfulfilled need in the. . .

inhibiting activity include the chick CAM assay, the mouse corneal assay, and the effect of administering isolated or synthesized proteins on implanted tumors. The chick CAM assay is described by O'Reilly, et al. in Angiogenic Regulation of Metastatic Growth Cell, vol. 79 (2), October 21,. . .

Cancer means angiogenesis-dependent cancers and tumors, i.e. tumors that require for their growth (expansion in volume and/or mass) an increase in the number and density of the blood vessels supplying. . .

Regression refers to the reduction of tumor mass and size.

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present invention also includes methods of treating or preventing angiogenic diseases and processes including, but not limited to, macular degeneration and tumors by stimulating the production of melanin, and/or by administering substantially purified melanin, or a melanin-associated compound, or a fusion protein containing the. . .

Passive antibody therapy using antibodies that specifically bind

melanin can be employed to modulate endothelial-dependent processes such as reproduction, development, and wound healing and tissue repair.

Antibodies specific for melanin, or a melanin-promoting compound, are made according to techniques and protocols well-known in the art. The  
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antibodies may be either polyclonal or monoclonal. The antibodies are utilized in well-know immunoassay formats, such as competitive and non-competitive immunoassays, including ELISA, sandwich immunoassays and radioimmunoassays (RIAs), to determine the. . .

limited to,

ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis; angiogenesis-dependent cancer, including, for example, solid tumors, blood born tumors such as leukemias,

and tumor metastases; benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; rheumatoid arthritis; psoriasis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; and. . .

cardiac muscle especially following transplantation of a heart or heart tissue and after bypass surgery, promotion of vascularization of solid and relatively avascular tumors for enhanced cytotoxin delivery, and enhancement of blood flow to the nervous system, including but not limited to the cerebral cortex and. . .

destruction of cells that bind melanin. These cells may be found in many locations, including but not limited to, micrometastases and primary tumors. Peptides linked to cytotoxic agents are infused in a manner designed to maximize delivery to the desired location. For example, ricin-linked high. . . antagonists may be co-applied with stimulators of angiogenesis to increase vascularization of tissue. This therapeutic regimen provides an effective means of destroying metastatic cancer.

a melanin-promoting compound, may be used in combination with other compositions and procedures for the treatment of diseases. For example, a tumor may be treated conventionally with surgery, radiation or chemotherapy combined with melanin, and then another anti-angiogenic compound may be subsequently administered to the patient to extend the dormancy of micrometastases and to stabilize any residual primary tumor.

the compound, the polymers being implanted in the vicinity of where drug delivery is desired, for example, at the site of a tumor or implanted so that the endostatin is slowly released systemically. Osmotic minipumps may also be used to provide controlled delivery of high. . . through cannulae to the site of interest, such as directly into a metastatic growth or into the vascular supply to that tumor.

Kits for measurement of melanin, or a melanin-promoting compound, are also contemplated as part of the present invention. Antisera that possess the highest titer and specificity and can detect the. . . and non-competitive assays, radioimmunoassay, bioluminescence and chemiluminescence assays, fluorometric assays, sandwich assays, immunoradiometric assays, dot blots, enzyme linked assays including ELISA, microtiter plates, antibody coated



immunocytochemistry. For each kit the range, sensitivity, precision, reliability, . . .

. . .  
in the pigmented layer of the eye,  
or choroid, compared to white patients. Additionally, black patients have a  
reduced incidence of vascular tumors in the skin such as  
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=> d ibib 7-12

L40	ANSWER 7 OF 12	PCTFULL	COPYRIGHT 2006 Univention on STN
ACCESSION NUMBER:		1997000892	PCTFULL ED 20020514
TITLE (ENGLISH):		DEPIGMENTING ACTIVITY OF AGOUTI SIGNAL PROTEIN AND PEPTIDES THEREOF	
TITLE (FRENCH):		ACTIVITE DE DEPIGMENTATION DE LA PROTEINE-SIGNAL D'AGOUTI ET SES PEPTIDES	
INVENTOR(S):		HEARING, Vincent, J., Jr.	

PATENT ASSIGNEE(S): THE GOVERNMENT OF THE UNITED STATES OF AMERICA,  
represented by THE SECRETARY DEPARTMENT OF HEALTH AND  
HUMAN SERVICES;  
HEARING, Vincent, J., Jr.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 9700892	A2	19970109

DESIGNATED STATES

W:

AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI  
GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD  
MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM  
TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ  
MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC  
NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1996-US10695 A 19960621  
PRIORITY INFO.: US 1995-60/000,436 19950623

L40 ANSWER 8 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN  
ACCESSION NUMBER: 1995009629 PCTFULL ED 20020514  
TITLE (ENGLISH): SYNTHETIC MELANIN  
TITLE (FRENCH): MELANINE SYNTHETIQUE  
INVENTOR(S): PAWELEK, John, M.  
PATENT ASSIGNEE(S): YALE UNIVERSITY  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 9509629	A1	19950413

DESIGNATED STATES

W:

AM AU BB BG BR BY CA CN CZ EE FI GE HU JP KE KG KR KZ  
LK LR LT LV MD MG MN MW NO NZ PL RO RU SD SI SK TJ TT  
UA UZ VN KE MW SD SZ AT BE CH DE DK ES FR GB GR IE IT  
LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD  
TG

APPLICATION INFO.: WO 1994-US10835 A 19940926  
PRIORITY INFO.: US 1993-131,270 19931001

L40 ANSWER 9 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN  
ACCESSION NUMBER: 1992018166 PCTFULL ED 20020513  
TITLE (ENGLISH): MELANIN-BASED AGENTS FOR IMAGE ENHANCEMENT  
TITLE (FRENCH): AGENTS A BASE DE MELANINE UTILISES POUR LE REHAUSSEMENT  
DES IMAGES  
INVENTOR(S): WILLIAMS, Robert, F.  
PATENT ASSIGNEE(S): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM;  
WILLIAMS, Robert, F.  
LANGUAGE OF PUBL.: English  
DOCUMENT TYPE: Patent  
PATENT INFORMATION:

NUMBER	KIND	DATE
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WO 9218166	A1	19921029

DESIGNATED STATES

W:

AT AU BB BE BF BG BJ BR CA CF CG CH CI CM CS DE DK ES  
FI FR GA GB GN GR HU IT JP KP KR LK LU MC MG ML MN MR  
MW NL NO PL RO RU SD SE SN TD TG US

APPLICATION INFO.: WO 1992-US3177 A 19920415  
PRIORITY INFO.: US 1991-685,937 19910415

L40 ANSWER 10 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN  
ACCESSION NUMBER: 1992007580 PCTFULL ED 20020513

TITLE (ENGLISH): THERAPEUTIC USES OF MELANIN  
TITLE (FRENCH): UTILISATIONS THERAPEUTIQUES DE LA MELANINE  
INVENTOR(S): BERLINER, David, L.;  
ERWIN, Robert, L.;  
McGEE, David, R.

PATENT ASSIGNEE(S): BIOSOURCE GENETICS CORPORATION

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9207580	A1	19920514

DESIGNATED STATES

W:

AT AU BE CA CH DE DK ES FI FR GB GR IT JP LU NL NO SE

APPLICATION INFO.:

WO 1991-US8213 A 19911105

PRIORITY INFO.:

US 1990-609,311 19901105

L40 ANSWER 11 OF 12

PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER:

1990012869 PCTFULL ED 20020513

TITLE (ENGLISH):

NON-MELANOCYTIC, EUCARYOTIC CELL CONSTITUTIVELY  
EXPRESSING BIOLOGICALLY ACTIVE HUMAN TYROSINASE AND USE  
THEREOF

TITLE (FRENCH):

CELLULE EUCARYOTE NON MELANOCYTIQUE EXPRIMANT DE  
MANIERE CONSTITUTIVE LA TYROSINASE HUMAINE  
BIOLOGIQUEMENT ACTIVE, ET SON UTILISATION

INVENTOR(S):

BOUCHARD, Brigitte;

HOUGHTON, Alan, N.

PATENT ASSIGNEE(S):

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

LANGUAGE OF PUBL.:

English

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9012869	A1	19901101

DESIGNATED STATES

W:

AT BE CA CH DE DK ES FR GB IT JP LU NL SE

APPLICATION INFO.:

WO 1990-US2288 A 19900426

PRIORITY INFO.:

US 1989-343,960 19890426

L40 ANSWER 12 OF 12

PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER:

1990011295 PCTFULL ED 20020513

TITLE (ENGLISH):

MELANIN-CONCENTRATING HORMONES AND METHODS OF  
TREATMENT USING SAME

TITLE (FRENCH):

HORMONES CONCENTRANT LA MELANINE ET PROCEDES DE  
TRAITEMENT UTILISANT DE TELLES HORMONES

INVENTOR(S):

VAUGHAN, Joan;

FISCHER, Wolfgang, Hermann;

RIVIER, Jean, Edouard;

NAHON, Jean-Louis, Marie;

PRESSE, Francoise, Genevieve;

VALE, Wylie, Walker, Jr.

PATENT ASSIGNEE(S):

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

LANGUAGE OF PUBL.:

English

DOCUMENT TYPE:

Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9011295	A1	19901004

DESIGNATED STATES

W:

AT BE CA CH DE DK ES FR GB IT JP LU NL SE

APPLICATION INFO.:

WO 1990-US1492 A 19900320

PRIORITY INFO.:

US 1989-326,984 19890322

=> d kwic 8

L40 ANSWER 8 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN  
TIEN SYNTHETIC MELANIN  
ABEN A melanin that is soluble in an aqueous solution at a pH  
between 5 and 9 at a temperature of 0  
to 100 &deg;C. Advantageously, the melanin is capable of being  
filtered through at least a 0.45 micron  
size filter, and has a molecular weight of greater than 10,000  
kilodaltons. The melanin is useful  
for providing a naturally-appearing tan to mammalian skin and hair. Such  
melanin can be produced by  
combining dopachrome and an appropriate enzyme, or by incubating  
5,6-dihydroxyindole-2-carboxylic  
acid alone or with 5,6-dihydroxyindole, or with 3-amino-tyrosine. The  
melanin is also useful for  
providing a sun-screen to mammalian skin and hair, to treat  
post-inflammatory hypo- and  
hyperpigmentation, to tint. . . as a coloring agent in foodstuffs  
such as coffee, tea, soda, whisky and liquors. Also  
included are self-tanning compositions containing melanin and  
DHA.

DETD . . . which absorb ultraviolet radiation and, thus,  
provide protection from its harmful effects, such as  
premature skin aging and the occurrence of skin cancers.

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5 Melanin. Science, 217:1163-1165, 1982;  
dopachrome tautomerase: John Pawelek, After  
Dopachrome?, Pigment Cell Research, 4:53-62, 1991,  
glycoprotein 75: Timothy M. Thomson, M. Jules Mattes,  
Linda Roux, Lloyd Old and Kenneth O, Lloyd,  
io Pigmentation-associated Glycoprotein of Human Melanomas  
and Melanocytes: Definition with a Mouse Monoclonal  
Antibody, J, Invest. Derm,, 85:169-174, 1985;  
MSH receptor: Seth J. Orlow, Sara Hotchkiss, and John  
M. Pawelek, Internal Binding Sites for MSH: Analyses in  
Wild Type and Variant Cloudman Melanoma Cells,, J, Cellular  
Physiology,, 142:129 136, 1990,  
The melanins according to the present invention can be  
admixed with a physiologically acceptable carrier to form a  
composition, which has the uses previously. . .

=> s wo2000010507/pn

L41 1 WO2000010507/PN  
(WO2000010507/PN)

=> s l41 and label?

131550 LABEL?  
L42 1 L41 AND LABEL?

=> d kwic

L42 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN  
PI WO 2000010507 A2 20000302

DETD The present invention also includes melanin, or a melanin-  
promoting compound, that can be labeled isotopically or with  
other  
molecules or proteins for use in the detection and visualization of  
melanin,

or a melanin-promoting compound, sites with. . .

Sci. USA 76,  
5217

Gavrieli, Y., Sherman, Y., and Ben-Sasson, S. A. (1992). Identification  
of  
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DNA

fragmentation. J. Cell Biol.. 119, 493

Good, D. J., Polverini, P. J., Rastinejad, F., Le Beau, M. M.,. . .

=>

---Logging off of STN---

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	38.59	102.24

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-2.25

STN INTERNATIONAL LOGOFF AT 14:28:47 ON 23 JAN 2006

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LOGINID:SSSPTA1642BJF

PASSWORD:

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NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	DEC 05	CASREACT(R) - Over 10 million reactions available
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NEWS	5	DEC 14	2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
NEWS	6	DEC 14	CA/CAPLUS to be enhanced with updated IPC codes
NEWS	7	DEC 21	IPC search and display fields enhanced in CA/CAPLUS with the IPC reform
NEWS	8	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS	9	JAN 13	IPC 8 searching in IFIPAT, IFIUDb, and IFICDB
NEWS	10	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC

NEWS 11 JAN 17 Pre-1988 INPI data added to MARPAT  
NEWS 12 JAN 17 IPC 8 in the WPI family of databases including WPIFV

NEWS EXPRESS JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,  
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.  
V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT  
<http://download.cas.org/express/v8.0-Discover/>

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\* \* \* \* \* STN Columbus \* \* \* \* \*

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=> file pctfull

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FULL ESTIMATED COST	0.21	0.21

FILE 'PCTFULL' ENTERED AT 14:54:31 ON 23 JAN 2006  
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FILE LAST UPDATED: 3 JAN 2006 <20060103/UP>  
MOST RECENT UPDATE WEEK: 200552 <200552/EW>  
FILE COVERS 1978 TO DATE

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USE IPC7 FORMAT FOR SEARCHING THE IPC. WATCH THIS SPACE FOR FURTHER DEVELOPMENTS AND SEE OUR NEWS SECTION FOR FURTHER INFORMATION ABOUT THE IPC REFORM <<<

=> s wo9834602/pn

L1 1 WO9834602/PN

=> s antibod? and l1

84196 ANTIBOD?

L2 1 ANTIBOD? AND L1

=> s l2 and melanin

2796 MELANIN

190 MELANINS

2854 MELANIN

(MELANIN OR MELANINS)

L3 1 L2 AND MELANIN

=> d l3

L3 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN  
 AN 1998034602 PCTFULL ED 20020514  
 TIEN MEDIATION OF CYTOKINES BY MELANIN  
 TIFR REGULATION DE LA PRODUCTION DE CYTOKINES PAR LA MELANINE  
 IN MOHAGHEGHPOUR, Nahid  
 PA BIOSOURCE TECHNOLOGIES, INC.  
 LA English  
 DT Patent  
 PI WO 9834602 A2 19980813  
 DS W: AU BG CA IL JP KR MX AT BE CH DE DK ES FI FR GB GR IE IT  
 LU MC NL PT SE  
 AI WO 1998-US2971 A 19980210  
 PRAI US 1997-8/798,846 19970212  
 ICM A61K031-195  
 ICS A61K031:40; A61K031:785

=> d ibib kwic

L3 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN  
 ACCESSION NUMBER: 1998034602 PCTFULL ED 20020514  
 TITLE (ENGLISH): MEDIATION OF CYTOKINES BY MELANIN  
 TITLE (FRENCH): REGULATION DE LA PRODUCTION DE CYTOKINES PAR LA  
 MELANINE  
 INVENTOR(S): MOHAGHEGHPOUR, Nahid  
 PATENT ASSIGNEE(S): BIOSOURCE TECHNOLOGIES, INC.  
 LANGUAGE OF PUBL.: English  
 DOCUMENT TYPE: Patent  
 PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9834602	A2	19980813

DESIGNATED STATES  
 W: AU BG CA IL JP KR MX AT BE CH DE DK ES FI FR GB GR IE  
 IT LU MC NL PT SE  
 APPLICATION INFO.: WO 1998-US2971 A 19980210  
 PRIORITY INFO.: US 1997-8/798,846 19970212  
 TIEN MEDIATION OF CYTOKINES BY MELANIN  
 PI WO 9834602 A2 19980813  
 ABEN Methods and compositions are provided that teach the use of purified  
 melanin compositions to  
 treat, prevent, or ameliorate diseases that are associated with excess  
 cytokine production. In  
 particular, methods and compositions are. . .  
 DETD MEDIATION OF CYTOKINES BY MELANIN  
 1 FIELD OF THE INVENTION  
 Methods and compositions are described for the use of purified  
 melanin to treat disease in animals and man. The disclosed  
 melanin  
 compositions are particularly useful for regulating cytokine production  
 by  
 mammalian and human cells both in vitro and in vivo.  
 . . .  
 syndrome a significant  
 .2 -  
 SUBSTITUTE SHEET (RULE 26)  
 medical problem. Taken together, these results provide a mechanistic  
 basis  
 for considering the use of melanin, an agent that interferes  
 with the  
 synthesis/release of IL-1, IL-6 and TNF-cc, for managing wasting in  
 patients.



AIDS-KS derived cells produce other cytokines including IL-1 (Marx, Science 248:442-443, 1990) Addition of anti-IL-1 antibody to KS cell lines also resulted in decreased cellular proliferation. The increased levels of serum IL-6 and polyclonal B cell activation may. . .

A wide variety agents have been used to combat inflammation and life-threatening aspects of cytokines. Anti-TNF- $\alpha$  antibody, the TNF- $\alpha$  receptor, anti-IL-6,, and IL-1 receptor antagonist (IL-1Ra) therapy were shown to reduce death after acute systemic toxicity (e.g., septic shock). .

agent, or the site of infection (Bagby et al., J. Infect. Dis. 163:83-88, 1991). Moreover, in a number of studies, anti-cytokine antibodies only partially protected the animals (Feingold et al., J.

Rheumatol. 20:259-262) monoclonal antibody, as well as soluble TNF- $\alpha$  receptors (Moreland et al., Arthritis Rheum. 37:S295, 1994), or soluble IL-1 receptor (Drevlow et al., Arthritis Rheum. 37:S339, 1994) is effective in the treatment of rheumatoid arthritis. However, use of soluble cytokine receptors or antibodies to a single factor is constrained by the presence of multiple cytokines that participate in the manifestation of inflammatory conditions. Moreover, the large-scale treatment with anticytokine antibody may lead to production of anti-idiotypic antibodies.

Melanin,, inter alia, is a free radical scavenger that acts as a bacterial virulence factor by protecting the organism from some host. . .

Additional studies have shown that melanin expression by bacteria may be a virulence factor that helps bacterial pathogens avoid the afferent phase of 25 T cell-mediated immune responses. . .

### 3.0, SUMMARY OF THE INVENTION

The present invention is directed to the use of melanin as a 30 therapeutic agent in animals, including humans. The preferred method of .7]

#### SUBSTITUTE SHEET (RULE 26)

treatment comprises the administration of purified melanin, or biosynthetic melanin, to an animal in an amount sufficient to alleviate or prevent an adverse symptom of disease or illness. Accordingly, an object of the invention is a method of using purified melanin to treat or prevent illness in a patient which comprises administering melanin to the patient in an amount sufficient to provide a therapeutic benefit to the patient.

In a preferred embodiment of the present invention, the purified

melanin provides a therapeutic benefit by being administered in an amount sufficient to modulate the immune response of the patient. In a particularly preferred embodiment, the purified melanin is administered in an amount sufficient to be associated with a decrease in host cytokine production, and in particular TNF- $\alpha$ , IL-1 and. . . decrease in cytokine production may be either a cause or effect of the beneficial clinical indications associated with the administration of purified melanins.

The purified melanins used in the presently described invention may also be administered in combination with a wide variety of pharmaceutically useful carriers or excipients. Accordingly, an additional embodiment of the present invention is the use of pharmaceutical compositions comprising purified melanin to reduce TNF-CC production or otherwise provide a therapeutic benefit to a patient.

An additional embodiment of the present invention is the use of highly purified melanins that have a substantially homogeneous structure, and are substantially free of incorporated contaminating amino acids or derivatives thereof.

The presently described therapeutic use of purified melanin is particularly deemed to be useful for the treatment of cachexia, sepsis, acute respiratory distress syndrome, cerebral malaria, rheumatoid arthritis, epithelial ulcers of. . .

. . . that graft rejection is often associated with an inflammatory response, an additional embodiment of the present invention is the use of purified melanin, or purified synthetic melanin, to reduce or prevent the rejection of transplanted organs and grafts. Similarly, the purified melanins are also deemed to be useful in the treatment and prevention of graft-versus-host disease.

. . . an additional embodiment of the present invention is a method of modulating cytokine production by an animal cell by administering purified melanin to said cell in an amount sufficient to modulate cytokine production by said cell. In a preferred embodiment, the purified melanin will have been tested in vitro to verify that compositions comprising the purified melanin have the property of being capable of modulating cytokine expression by mammalian or other animal cells.

#### 4,0. DESCRIPTION OF JUE FIGURES

Figure 1 shows that melanin inhibits LPS-induced TNF- $\alpha$  production. Open circles depict TNF- $\alpha$  production/release by monocytes ( $1 \times 10^6$  cells/ml) that were incubated for 40 min at 37°C with various concentrations of melanin AHM 8 before stimulation with 1 ng/ml LPS.

The TNF- $\alpha$  concentration was also determined for supernatants collected

from monocytes stimulated with LPS in the absence of melanin (3,230 pg/ 106 cells/ml), and from supernatants collected from monocytes maintained in medium alone (36 pg/ 106 cells/ml).

Closed circles depict the effect of melanin on the constitutive synthesis of protein by melanin-treated cells. Monocytes ( $1 \times 10^6$  per 0.2 ml leucine-free medium supplemented with 10% dialyzed human AB serum) were seeded in 96-well plates were incubated for 5 hr at 37°C with the indicated concentrations of melanin AHM 8. Control cells were maintained in medium alone for the duration of culture. At 4 hours prior to harvest, cells were.

Figures 2(A-D) show that melanin significantly inhibits production of TNF- $\alpha$  (Fig. 2A), IL-12 (Fig. 2B), and IL-6 (Fig. 2C), but not GM-CSF (Fig. 2D), by human peripheral blood monocytes. Monocytes were pretreated with the indicated concentrations of melanin AHM 8 (0  $\mu$ g/ml, open bar; 50  $\mu$ g/ml, slashed bar; 100  $\mu$ g/ml, solid bar) before stimulation with 1 ng/ml LPS. Controls included (1) melanin-nontreated cells stimulated with LPS, (2) melanin-treated, LPS-nonstimulated monocytes, and (3) monocytes incubated in complete medium in the absence of additives.

mean ( $\pm$ SEM) cytokine contents in the supernatant collected from 106 LPS-nonstimulated monocytes incubated in the presence of 0, 50, or 100  $\mu$ g/ml melanin were, respectively,  $<108 \pm 5$  pg/ml, for TNF- $\alpha$ ;  $<75 \pm 53$  pg/ml for IL-12;  $598 \pm 238$  pg/ml for IL-6; and  $<168 \pm 124$  pg/ml.

Figures 3(A & B) show duplicate experiments which indicate that the observed reversal of melanin-mediated suppression of TNF- $\alpha$  production is time-dependent. Human peripheral blood monocytes were incubated at 37°C with 100  $\mu$ g/ml melanin AHM 8. After a 1 hour incubation, cells were washed to remove free melanin, suspended in fresh medium, and stimulated with 1 ng/ml LPS at the indicated time points. The concentration of TNF- $\alpha$  in culture supernatants.

Figure 4 shows that melanin treatment suppresses TNF- $\alpha$  production even when applied after LPS stimulation. Monocytes were stimulated with 1 ng/ml LPS either 1 hour after (open box), simultaneously with (slashed box), or 1 hour before (solid black box) the addition of the indicated amount of melanin (50 or 100  $\mu$ g, respectively).

Control monocytes were incubated without LPS in either the absence or presence of melanin (not shown). Twenty-four hours after stimulation with LPS, the levels of TNF- $\alpha$  in the culture supernatants were measured

by  
ELISA. At both concentrations, the amount TNF- $\alpha$  inhibition observed  
was  
greatest when the cells were pretreated with melanin, followed  
by cells  
simultaneously treated with melanin and LPS, and cells treated  
with after  
is LPS stimulation ( $p < 0.05$  when compared to TNF- $\alpha$  production by  
monocytes treated for 1 hour with melanin before stimulation  
with LPS).

Figure 9(A-C) shows that melanin strongly inhibits the TNF- $\alpha$   
response in BALB/c mice. Circulating plasma concentrations of TNF- $\alpha$   
were measured by ELISA 90 min after i.v. injection. . . min before  
(19 mice);  
simultaneously with (40 mice); or 15 min after (18 mice) LPS injection.  
The  
concentrations of TNF- $\alpha$  in the melanin treated group and  
nontreated  
controls (open bars) were compared by the two tailed Mann-Whitney Test  
30 using the INSTATO 2.03 program. Results. . .

#### SUBSTITUTE SHEET (RULE 26)

#### , 0, DETAILED DESCRIPTION OF TT-1E INVENTION

The present invention is broadly directed to the discovery that  
melanin is useful for the therapeutic treatment of disease in  
animals,  
5 including humans.

In one embodiment, the melanins used in the presently  
described  
invention are substantially pure. In general, the term substantially  
pure

melanin shall refer to melanin preparations that are  
comprised of at least  
about 75 percent of the desired melanin, specifically at least  
about 85 percent,  
more specifically at least about 90 percent, and preferably at least  
about 95  
weight percent.

As a consequence of normal melanin production, a wide variety  
of  
protein and amino acid contaminants are typically incorporated into  
naturally occurring melanins. Additionally, the wide variety  
of substrates  
and contaminants that are typically available during normal  
melanin  
production in vivo may lead to the production of melanins with  
amorphous composition. Similarly, the wide variety of contaminants that  
are typically found in commercially available preparations of  
tyrosinase, the  
enzyme that makes melanin, are often incorporated into  
melanins  
produced in vitro.

Where pharmaceutical applications of melanin are contemplated,  
melanin products with defined and predictable compositions and  
structural  
features are highly desirable, and may even be necessary. Additionally,  
the  
contaminating proteins, and amino acids contained therein, that are  
often  
incorporated into naturally occurring or previously described

melanins may  
also prove immunogenic in the host. Thus, melanin preparations  
that are  
to be administered in vivo shall preferably be substantially free of  
contaminating proteins, amino acids, and especially toxins of. . .

The term 'biosynthetic melanin shall refer to melanin  
that is

.14 -

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produced by a recombinantly expressed and/or purified tyrosinase protein  
that has been provided with a substrate for melanin  
production. By  
producing melanin using high specific activity tyrosinase in  
conjunction  
with defined substrates, melanins are produced with  
substantially more  
uniform structure and composition than melanins typically  
found in  
nature. With proper methods of synthesis, the resulting biosynthetic  
melanins may also be substantially pure, or further processed  
to produce  
biosynthetic melanin preparations that are substantially pure.  
In the  
majority of instances, suitably processed biosynthetic melanin  
may replace  
10 naturally occurring melanin in any of the embodiments  
described herein.

The purified or biosynthetic melanins used in the present  
invention  
may optionally be characterized by being substantially free of  
contaminating  
amino acid content. For the purposes of the present invention,. the term  
substantially amino acid free shall refer to melanin  
preparations that  
15 generally contain less than about 10 percent amino acid content by  
weight,  
preferably less than about 7.5 percent amino. . . about 5 percent  
amino acid content, and specifically less than 2.5  
percent amino acid content by weight. Moreover,, compositions comprising  
purified biosynthetic melanins shall generally be  
substantially free of  
20 potentially toxic contaminants of bacterial origin such as, but not  
limited to,  
bacterial endotoxins (particularly. . .

Where the therapeutic use of the presently described purified  
melanins is contemplated, the purified melanin is  
preferably administered  
25 in a pharmaceutically acceptable carrier, via oral,, intranasal,,  
rectal,, topical,,  
intraperitoneal, intravenous,, intramuscular,, subcutaneous,, subdermal,  
transdermal, intrathecal, or intracranial methods, and the like.  
Typically,  
the preferred formulation for the purified melanin will vary  
depending  
upon the region of the host requiring treatment.

For example, topical immune reactions are preferably treated or  
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prevented by melanin formulations designed for topical  
application,

whereas systemic reactions are preferably treated or prevented by administration of compositions formulated for parenteral administration.

Additionally, immune-mediated disorders of the pulmonary system may be treated both parenterally and by direct application of the therapeutic melanin compositions to the respiratory system by inhalation therapy.

Additionally, local immune reactions, i.e., arthritic or inflamed joints, etc., may be treated by localized injection purified melanin compositions into the synovial capsule. Optionally, such local administration of purified melanin compositions may be performed in conjunction with corticosteroids.

Additionally, the purified melanin may be loaded into lipid-associated structures (i.e., liposomes, or other lipidic complexes) which may enhance the pharmaceutical characteristics of the purified melanin. The lipid-melanin complex may subsequently be targeted to specific target cells by the incorporation of suitable targeting agents (i.e., specific antibodies or receptors) into the melanin/lipid complex. Optionally, the purified melanin may be directly complexed with a targeting agent to produce the desired effect.

Where melanin mediated treatment of inflammatory disorders of the digestive tract and alimentary canal are contemplated, lipid formulations (e.g., emulsions, n-droemulsions, liposomes, etc.) comprising purified melanin may significantly protect the melanin from the digestive process. Accordingly, melanin formulations are contemplated that may be orally administered. To the extent that additional enteric protection is desired, for added protection, it. . . -  
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capsules (for example of soft or hard gelatin, which are themselves optionally additionally enteric coated. Alternatively, solid formulations comprising melanin may be treated more flexibly. They may either be coated with enteric materials to form tablets or they can be filled. .

Additionally, any of a variety of stabilizing agents may be utilized in  
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conjunction with the described melanin compositions. Although the melanin itself may function as an antioxidant, the oxidation of melanin or other components of the described compositions may be substantially reduced by preparing formulations in accordance with the present invention under an inert. . .

Formulations comprising purified melanin may also be stabilized for

15 storage and shipment by any of a number of well established methods, including but not limited to. . .

Where one seeks to augment long-term stability by freezing or freeze-drying

melanin compositions, suitable excipients may be added to the melanin comprising preparations prior to freezing. Examples of such stabilizing excipients include, mono or disaccharides (e.g., glucose, sucrose, etc.), polysaccharides, or any of. . .

the terms

treatment, therapeutic use, or medicinal use used herein shall refer to any and all methods of using the described purified melanin compositions to remedy a disease state or symptoms, or otherwise prevent,

30 hinder, retard, or reverse the progression of disease or any. . .

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undesirable symptoms in any way whatsoever. Similarly, a therapeutically effective amount of melanin is an amount sufficient to remedy a disease

state or symptoms, or otherwise prevent, hinder, retard, or reverse the progression of disease. . .

and interleukins including,

but not limited to, IL-1 and IL-6) production, in a particularly preferred

embodiment of the present invention, the purified melanin is used at a

dose that reduces or inhibits the excess production of TNF- $\alpha$  while still

allowing or facilitating an effective host. . .

When used in the therapeutic treatment of disease, an appropriate dosage of purified melanin, or modified form thereof, may be determined

by any of several well established methodologies. For instance, animal studies are commonly used to. . .

The presently described purified melanins may also be complexed

with molecules that enhance their in vivo attributes. Examples of such molecules include, but are not limited to,. . .

Additionally, the purified melanins may be complexed with a variety

of well established compounds or structures that,, for instance, further enhance the in vivo stability of the melanin, or otherwise enhance its

15 pharmacological properties (e.g., increase in vivo half-life, reduce toxicity, enhance solubility or uptake, etc.). Examples of such. . .

Where diagnostic, therapeutic or medicinal use of purified melanin,

20 or derivatives thereof, is contemplated, the melanin may generally be

prepared and maintained under sterile conditions that minimize that risk

off or avoid, microbial contamination. Because of the relatively small size

and inherent stability of purified melanin, compositions

comprising

melanin may also be sterile filtered prior to use. In addition to the above 25 methods of sterile preparation and filter sterilization, antimicrobial agents may also be added to the melanin compositions. Antimicrobial agents which may be used, generally in amounts of up to about 3% w/v, preferably from about 0.5 to 2.5%, . . . cresol, p-chloro-m-cresol, chlorobutanol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate and benzylalkonium chloride. Preferably, antimicrobial additives will either enhance the biochemical properties of the melanin, or will be inert with respect melanin activity. To the extent that a given antimicrobial agent may prove deleterious to melanin activity, another agent may be substituted which effects the desired functions of melanin to a lesser extent.

One embodiment of the presently claimed methods relates to the use of purified melanin to modulate the immune system. Such modulation is deemed to be a function of melanin's ability to either directly or indirectly effect cytokine expression or activity in vivo or in vitro. In a preferred embodiment, the therapeutic use of melanin will downregulate cytokine expression. Melanin's ability to downregulate cytokine expression may also be exploited by using melanin in conjunction with established therapeutics in order to reduce the severity of the adverse immune-related reactions associated with a given therapeutic. For example, IL-2 treatment has been associated with adverse systemic consequences that are often dose dependent. Because of melanin's ability to modulate adverse immune reactions, the use of melanin in conjunction with cytokine may allow for the clinical use of higher systemic concentrations of cytokine. Accordingly, an additional embodiment of the present invention is the use of purified melanin to reduce the toxic side-effects of therapeutic agents.

adverse disease consequences have been linked with 25 excess TNF-(x production, in a particularly preferred embodiment of the present invention, the purified melanin is used at a dose that reduces or inhibits the excess production of TNF-cc while still allowing or facilitating an effective host. . . .

Given that melanin is useful for treating the wasting syndrome that is often associated with acquired immunodeficiency syndrome (AIDS), or cancer, the presently described methods. . . .

An additional embodiment of the present invention is the use of purified melanin to treat allergy related hypersensitivity



reactions.

Particularly contemplated is the use of purified melanin to prophylactically treat individuals that may be susceptible to the adverse consequences of allergic reactions such as, but not limited to, drug reactions, insect stings,, dermatitis,, food allergies,, and the like. Additionally contemplated is the intervening use of purified melanin to alleviate or reduce the adverse symptoms of allergic reactions.

Melanin is a virulence factor that contributes to the pathogenesis of a variety of infectious agents. To the extent that melanins that are 30 characteristic of a particular pathogen may be identified, an additional aspect

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of the presently claimed invention is the use of purified melanin, or portions or analogues thereof, as vaccines to prevent progression and spread of melanin producing pathogens.

Similarly, the identification and use of melanoma associated or specific melanins is contemplated to provide an additional form of cancer therapy comprising the use of tumor specific melanins, or fragments or analogues thereof, as cancer vaccines, or tumor-specific immunostimulants.

Additionally, the identification of pathogen or tumor specific melanins shall be useful for the identification or production of receptors, ligands, or polyclonal or monoclonal antibodies that specifically bind to the pathogen or tumor specific melanin. Accordingly, an additional embodiment of the present invention are receptor, ligand, or antibody-based diagnostics or therapeutics that target pathogen or tumor specific melanins, or the cellular receptors therefore.

#### 6 Synthesis of Water-Soluble Melanin

Water soluble melanin was produced and prepared for use essentially as described in U.S. Patent Nos. 5,340,734; 5,466,592; 5,486,351; 5,210,076 and 25 5,057,325 herein incorporated by reference. Melanins produced using the described methods were further purified by acid precipitation by addition of concentrated HO ]pH 1 Precipitated melanin was recovered by centrifugation.

When analyzed for purity, the resulting melanin (designated AHM 8) 30 was found to comprise about 96% percent of the final product by weight.

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The amino acid content of melanin AHM 8 was less than 4.2%. The total amino acid was 8.4% by weight of which 4.38% was tyr + gly. The elemental analysis yielded the following: %C=51.01; %H=3.74; %N=9.5; %S=0; and %O=33

The endotoxin content of melanin AHM 8 was estimated using the chromogenic Limulus amoebocyte lysate (CLAL) test kit (BioWhittaker, Inc., Walkersville, MD). To determine whether AHM 8 . . . content of the mixture was determined using the CLAL test according to the manufacturer's directions. Percent reduction in the endotoxin content of melanin-containing standard preparation was calculated as follows.

. . .  
50 µg/ml AHM 8 produced 22% reduction in the activity of the endotoxin standard. As shown in Table 1, the endotoxin content of melanin AHM 8, at 50 µg/ml, was only 0.069 endotoxin unit (EU)/ml. Under our experimental conditions, the production of TNF-α by human peripheral blood . . .

#### 6.2, Pretreatment With Melanin Suppresses LPS-Induced TNF-α Production

The effect of biosynthetic melanin on in vitro TNF-α production was evaluated by comparing the levels of TNF-α in the culture supernatants of

melanin-treated and nontreated monocytes following stimulation with

LPS. In these experiments, monocytes, ( $1 \times 10^6$ /ml), were incubated with various doses of melanin at 37°C in a humidified atmosphere containing

5% CO<sub>2</sub>. Following a 30-60 min incubation, monocytes were stimulated  
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with LPS in the continuous presence of melanin. Controls included (1)

melanin-nontreated cells stimulated with LPS; (2)

melanin-treated, LPS-

nonstimulated monocytes; and (3) monocytes incubated in complete medium in the absence of additives. Twenty-four hours after stimulation with LPS, the levels . . .

As shown in Figure 1, treatment of monocytes with melanin AHM 8 resulted in a dose-dependent inhibition of LPS-induced TNF-α production.

To ensure that the presence of melanin in the culture supernatants did not interfere with the assay (ELISA), the TNF-α concentrations in the supernatants collected from melanin-treated monocytes were determined from two standard curves. For construction of the control standard curve, TNF-α standards were diluted in complete culture medium. . .

Melanin-containing standard curves were constructed by plotting optical density (O.D.) values obtained from TNF-α standards (over a range from 0 to 1,000 pg/ml) that were diluted in complete medium incubated with 0-50 µg/ml melanin for 24 hours at 37°C. In parallel assays, the TNF-α content of

culture supernatants collected from monocytes that were treated with 0-50 gg/ml melanin before stimulation with LPS (referred to hereafter as the test samples) were determined by reading their O.D. against each standard 30 curve.. . .

As shown in Table 3, SI values of supernatants collected from melanin-pretreated monocytes were consistently lower than the SI values of supernatants collected from cells were not exposed to melanin. Taken 10 together, these data indicate that melanin suppresses LPS-induced TNF- $\alpha$  synthesis/release by human monocytes and that this reduction is not the consequence of an inhibitory effect of melanin on the assay system.

TABLE3

is INFLUENCE OF MELANIN ON TNF- $\alpha$ -SPECIFIC ELISA'

Melanin TNF- $\alpha$  Content of Culture Supernatants

Content of from Cells Treated with AHM 8 (gg/ml)

TNF-(x

Standard

0 10 25 50

(Stimul

ation

Index1

78

39 17 7

69

35 16 7

82. . .

63\* The Effect of Melanin on Protein Synthesis by Human Peripheral Blood Monocytes

To determine whether melanin selectively interferes with the production of LPS-induced cytokines, the effect of melanin AHM 8 on

constitutive protein synthesis by human monocytes was measured. Protein synthesis was measured by incorporation of [ $^3$ H]leucine. Monocyte protein 10 synthesis after 5 hours incubation in the presence of 100 [tg/ml melanin

AHM4 8 was roughly comparable to that displayed by melanin nontreated

control cells (23% lower). Under parallel experimental conditions incubation of monocytes with 20 4g/ml cycloheximide resulted in complete is inhibition of [ $^3$ H]-leucine. . .

incorporation in monocytes incubated for

20 20 hours in the presence of 100gg/ml AHM 8 was also comparable to that of

the melanin nontreated cells (32,775  $\pm$ 1,977 cpm versus 29,713  $\pm$ 856 cpm).

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Melanin Selectively Suppresses Cytokine

Production by Human Monocytes

To determine whether melanin suppresses the production and release of other LPS-induced cytokines, peripheral blood monocytes were tested (essentially as described above) for the ability to produce TNF- $\alpha$ , IL-19,

IL-6 and granulocyte/macrophage-colony stimulating factor (GM-CSF) after melanin treatment. The levels of TNF-(x, IL-19, and GM-CSF in

the culture supernatants were measured, in duplicate, using ELISA kits purchased from Biosource. . . .

with AHM 8 produced significantly ( $p < 0.05$ ) lower levels of TNF-cc, IL-1p, and IL-6 than did their respective controls. Under parallel conditions, melanin did not inhibit production or release of GM-CSF by LPS stimulated monocytes. In contrast, monocytes pretreated with 30 100 gg AHM. . . . SHEET (RULE 26) following stimulation with LPS ( $p < 0.01$ ). This indicates that AEM 8 does not inhibit LPS signalling. The finding that melanin does not suppress GM-CSF secretion is of particular interest. GM-CSF affects the intracellular phosphorylation of nucleoside analogues in monocytes and macrophages, 5. . . .

#### 6,5, Continuous Presence of Melanin Is Not Required for S of TNF-a Production

To determine whether suppression of TNF-a production requires the continuous presence of melanin, freshly isolated human monocytes (jx106 cells/ml of complete medium) were treated with inhibitory concentrations of melanin AHM 8. Following a 1 hr incubation at 37'C, monocytes in one set of culture were stimulated with LPS in the continuous presence of is melanin. Monocytes in a second set of cultures were washed once by low-speed centrifugation before stimulation with LPS. Controls included (1) melanin-nontreated cells stimulated with LPS; (2) melanin-treated, LPS-nonstimulated monocytes; and (3) monocytes incubated in complete medium in the absence of additives. Twenty-four hours after stimulation 20 with LPS, the levels of TNF-a in the culture supernatants were measured in duplicate, by ELISA. Suppression of TNF-cc production did not require that melanin be continuously present. In fact, TNF-(x production was suppressed by 63% even after the melanin had been washed out of the 25 culture immediately before stimulation with LPS (data not shown).

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#### \*6, Melanin-Mediated Suppression of TNF-a Production Is Reversible

To allow time for recovery, monocytes pretreated with the inhibitory concentrations of melanin AHM 8 were incubated for 2-18 hours in complete medium before stimulation with LPS. For each time point, the following cultures served as control: (1) melanin-nontreated, LPS-stimulated; (2) melanin-nontreated, LPS-nonstimulated; and (3) melanin-treated, LPS-nonstimulated monocytes. The concentration of TNF-(x in the culture supernatants was measured 24 hours after the addition of LPS.

Data from two experiments, shown in Figure 3(A & B), demonstrate that melanin-mediated suppression of TNF-a persisted at least for 7 hours.

The suppressive effects of melanin were reversed upon short-term culture.

Monocytes stimulated with LPS 18 hours after removal of melanin exhibited a higher TNF- $\alpha$  response (44-47% decrease in TNF- $\alpha$  release versus a 74-88% reduction after a 7-hour AHM 8 washout period). These data indicate that monocytes treated with 100  $\mu$ g/ml melanin AHM 8 were not killed under these experimental conditions and that recovery from melanin-mediated suppression is time-dependent.

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,7\* Melanin Suppresses Production of TNF- $\alpha$  by Activated Monocytes

The data presented in the preceding sections are from experiments in which monocytes were pretreated with melanin AHM 8 before LPS stimulation. To determine whether melanin suppresses production of TNF- $\alpha$  even when it is administered after LPS-stimulation, monocytes were treated with melanin either 1 hour after, simultaneously with, or 1 hour before stimulation with LPS. As expected, melanin added 1 hour before LPS drastically inhibited LPS-induced TNF- $\alpha$  production (84  $\pm$  4% inhibition at 100  $\mu$ g/ml) (Figure 4). When melanin was added 1 hour after LPS stimulation, a partial suppression of TNF- $\alpha$  response was observed (45  $\pm$  13% inhibition at 100  $\mu$ g/ml,  $p=0.05$ ). Melanin added at earlier time points following LPS stimulation did not exert a stronger suppressive effect.

15 Treatment of monocytes with 100  $\mu$ g/ml melanin either 7.5 or 60 min after LPS stimulation reduced TNF- $\alpha$  production by 50% and 52%, respectively (not shown). These data indicate that melanin may provide a corrective benefit as well as a preventative benefit, and may also indicate that at least two separate mechanisms are responsible for the net reduction in TNF- $\alpha$  production seen after prior exposure to melanin.

The finding that melanin appears less effective at suppressing TNF- $\alpha$  secretion by activated monocytes is of particular interest because this cytokine is an essential mediator in the immune response. This finding suggests that melanin could be used to reestablish a balanced or normal level of TNF- $\alpha$  in patients with wasting syndrome without destroying the patient's ability. . .

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,8, Effect of Melanin on TNF- $\alpha$  Production Induced by Additional Stimuli

To test whether AHM 8 has the ability to modulate TNF- $\alpha$  production by cells that have. . .

6e9 Effect of melanin on the expression of TNF- $\alpha$  mRNA

Northern blot hybridization (Chomczynski and Sacchi, Anal.

6 Effect of Melanin on TNF- $\alpha$  Production In Vivo

To determine whether melanin reduces cytokine production in vivo, circulating concentrations of TNF- $\alpha$  were measured in mice that had been  
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injected with. . .

1987). Therefore, the in vivo TNF- $\alpha$  response to LPS was used as a model to determine the cytokine regulatory effects of melanin.

(0.625 mg/Kg) and 50 mg  
20 AHM 8/Kg body weight (Acute toxicity studies showed that a single Lv. dose  
of 5 g/kg melanin was well tolerated by Sprague Dawley rats).  
Control mice  
received either LPS, AHM 8, or PBS. A PBS sham injection was. . .

Results from two subsequent experiments showed that plasma TNF- $\alpha$  levels in mice injected with 50 mg/kg melanin 60 min before challenge with LPS was 77% lower than those injected with LPS alone (Figure 9A,  $p < 0.001$ ). The concentration of TNF- $\alpha$  in the plasma of 10 mice given either melanin alone or PBS (the vehicle) was  $33 \pm 16$  and  $45 \pm 17$  pg/ml, respectively.

62% ( $n = 40$ ) when mice were injected concomitantly with LPS and 50 mg/Kg AHM 8 (Figure 9B,  $p < 0.0001$ ). Melanin was also inhibitory at 25 mg/Kg. The plasma TNF- $\alpha$  concentration in 12 mice injected concomitantly with 0.625 mg/Kg LPS and 25 mg/kg. . .  $4,473 \pm 1,913$  pg/ml,  $p = 0.05$ ). The inhibitory effect exerted by AHM 8 was not due to direct interaction of melanin with LPS because in these experiments mice were first injected in one tail vein with LPS and immediately into a second tail. . .

Melanin was also effective when administered 15 min after LPS challenge. As shown in Figure 9C, the levels of circulating TNF- $\alpha$  in mice  
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injected with melanin 15 min after LPS administration was significantly ( $p = 0.008$ ) lower than the corresponding controls injected with LPS alone.

However, melanin was incapable of down regulating TNF- $\alpha$  production/release when injected 30 min after LPS insult (data not shown).

in mice (Garina et al. J. Exp. Med. IM:1305-1310,1991), and suggest that once the posttranscriptional phase of TNF- $\alpha$  biosynthesis has been completed, melanin is incapable of downregulating the process.

Taken together these data indicate that melanin significantly reduces

TNF- $\alpha$  production/release under acute inflammatory condition and that there is no need for pretreating the animals to achieve the protective effect of melanin.

have been specifically exemplified in the above in 15 vivo studies, typically, any acceptable animal model may be used to assess purified melanin's ability to modulate cytokine expression in vivo.

and the mode of injection. Accordingly, the following disclosure provides an example of 20 an in vivo study where prior treatment with melanin provides prophylactic protection against subsequent challenge with endotoxin. The following example is provided solely for purposes of exemplification and should not be deemed. . .

Purified melanin (AHM 8) is usually injected i.v. and is generally

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introduced into test animals at a concentrations. . .

Following melanin treatment, the various control and test subjects are injected with a variety of sub-lethal and lethal doses of mitogen (LPS, or other. . . systemic sepsis or shock). Blood samples are drawn at suitable time intervals after introduction in order to quantify the amounts of purified melanin and 10 cytokine that are present in the bloodstream. Alternatively, where lethal doses of mitogen are used, the extent to which melanin confers protection to the test animals is determined.

CLMEN 1 A method of modulating cytokine production by an animal cell, comprising: administering purified melanin to said cell in an amount sufficient to modulate cytokine production by said cell.

8 A method of modulating cytokine production by an animal, comprising administering purified melanin to said animal in an amount sufficient to alleviate or reduce an adverse symptom of a disease associated with cytokine expression.

18 A method of reducing the systemic toxicity of a therapeutic agent comprising administering purified melanin to an individual in an amount sufficient to reduce or alleviate an adverse symptom associated with said 20 therapeutic agent.

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L3 1 S L2 AND MELANIN

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DETD Similarly, the identification and use of melanoma associated  
or  
specific melanins is contemplated to provide an additional form of  
cancer  
therapy comprising the use of tumor specific melanins, or. . .

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